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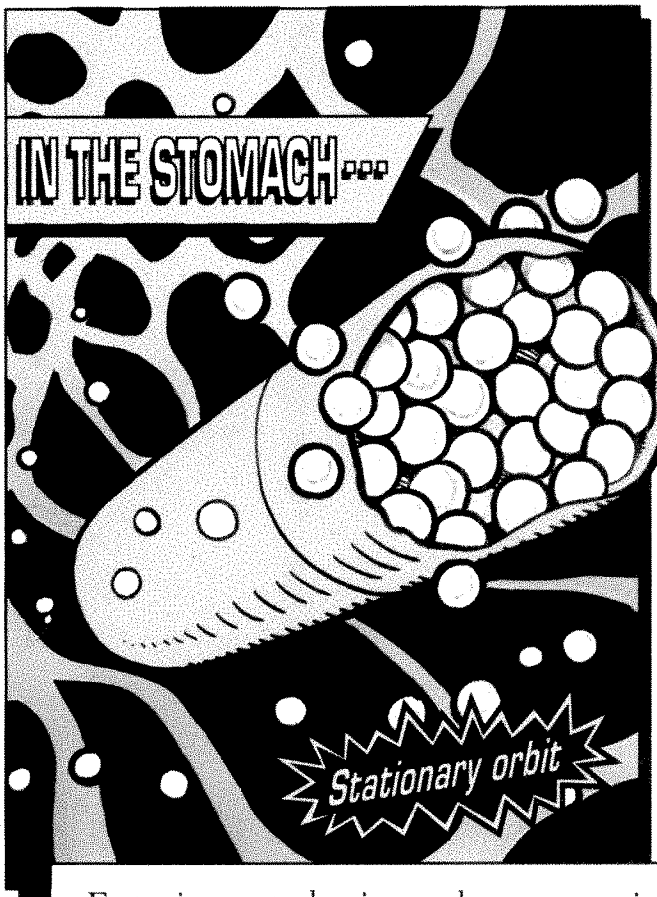

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1. Stead RJ et al. *Thorax* 1987;**42**:533-537. 2. Beverley DW et al. *Arch Dis Child* 1987;**62** 564-568.

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## Cover picture

### The Association of Surgeons of Great Britain and Ireland

The Association of Surgeons of Great Britain and Ireland was founded in 1920 by a group of leading surgeons of the day. The guiding spirit and inspiration behind the concept was Berkeley Moynihan, later Lord Moynihan of Leeds, who had been struck by the lack of cohesion among surgeons as early as 1909. He wrote that 'surgeons in one town knew little or nothing of surgeons elsewhere. A surgeon from Manchester had never visited an operation theatre in Leeds, nor had ever been asked in consultation. As a consequence it was not infrequent to have to listen to disparagement of one surgeon by another; and jealousies, openly expressed, were too often heard'. The founding objectives of the Association, therefore, were twofold – the advancement of the science and art of surgery and the promoting of friendship amongst surgeons.

The first meeting was held in London under the presidency of Sir John Bland-Sutton, the second in Edinburgh and the third in Leeds under the presidency of Moynihan himself. In 1924 a Presidential Badge was presented to the Association by Sir Berkeley Moynihan. The centre of the badge is occupied by a head of Lord Lister in low relief in an octagonal reed frame. Surrounding this are two branches of delicately carved oak with interlaced ribbon bearing the title 'The Association of Surgeons of Great Britain and Ireland'. Above the branches appear the coats of arms and crests of Lister and Moynihan, the whole of these surrounding details being minutely pierced. A gold collar with 34 links bears the names of the various Presidents. When the links were exhausted, a hinged gold plate was inserted behind the jewel, on which the names of the Presidents are now inscribed. The badge is made of hand chiselled 18 carat gold and weighs 6¾ ounces troy.

Initially, the Fellowship was limited to 250 consultants. Women were first admitted in 1936 and in 1953 Associate Fellowship was introduced for a limited number of trainee surgeons. In 1970, 50 years after its foundation, the Fellowship was opened to all Consultant Surgeons and more recently, through links with the Association of Surgeons in Training, all Senior Registrars have been eligible for Affiliate Fellowship.

Meetings of the Association have been held in many centres in England, Wales, Scotland and Ireland. Future meetings are planned in purpose-built conference centres in Jersey (1992), Birmingham (1993), Harrogate (1994) and, in celebration of the 75th Anniversary of the Association, in London (1995). In recent years there have been additional Autumn meetings held overseas; successful visits have been made to Calgary, Barcelona, Copenhagen, Australia and Amsterdam.

In 1992 the Association will participate in the second Eurosurgery meeting in Brussels on 2–5 June, the Quatercentenary Celebrations of Trinity College, Dublin on 20–24 September and in 1993 participate in the third Eurosurgery meeting in London on 15–18 September.

The Association is the specialty association for general surgery, representing 946 Consultant Surgeons and is recognised as such by government as well as the profession.

**Bernard Ribeiro**
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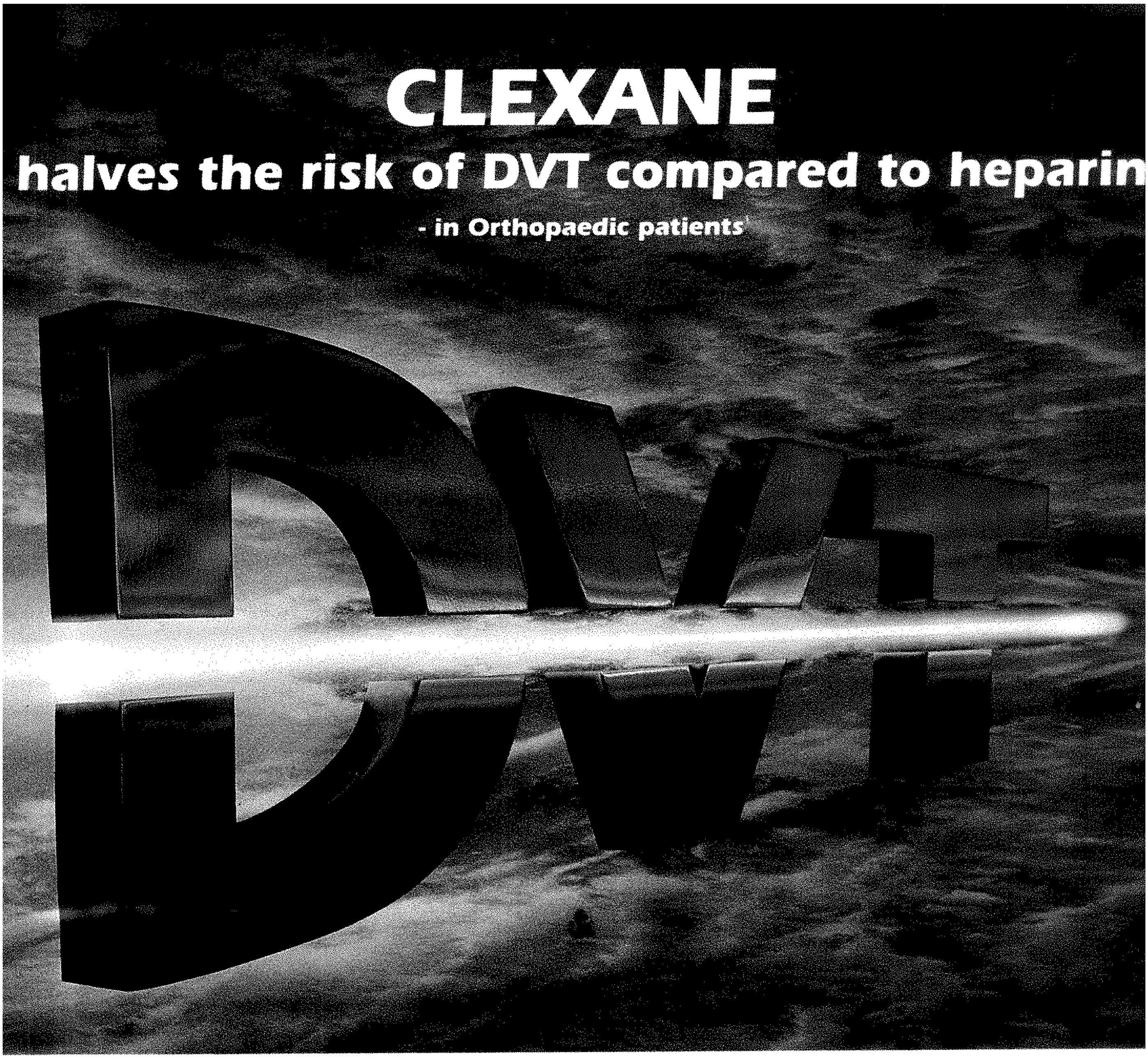
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Original articles should normally be in the format of introduction, methods, results, discussion. Each manuscript should contain a summary on a separate page. Authors are reminded that there is considerable pressure on editorial space in the Journal. Lengthy manuscripts are likely to be returned to authors for shortening. The discussion in particular should be clear and concise, and should be limited to matters arising directly from the results. Authors should avoid discursive speculation.

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methods, results and discussion. These sections should run sequentially through the text, avoiding blank space between them.

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The title page should give. (1) the title of the article; (2) the name and initials of each author, (3) the department and institution to which the work should be attributed; (4) the name and address of the author responsible for correspondence and to whom requests for reprints should be addressed; (5) sources of financial support; and (6) the category in which the manuscript is being submitted (original article, case report etc.).

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The second page of the manuscript should carry a summary of not more than 150 words. It should embody the purposes of the study or investigation, basic procedures (study material and observational and analytical methods), main findings (with specific data and their statistical significance, if possible) and the principal conclusions.

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Three copies of all illustrations and tables should be submitted. Each table with an appropriate brief title should be typed on a separate page. At least one set of illustrations (line drawings, radiographs, photomicrographs etc.) should be submitted in the form of glossy prints, original transparencies, or negatives and should not be mounted. Photocopies should be of sufficient quality to enable the Journal's referees to judge their content and value. Each illustration should have a label pasted on the reverse side giving its number (to correspond with its reference in the text) and the name(s) of the author(s); the top of the illustration should be indicated. Illustrations should be drawn and labelled appropriately for reduction to one or two column widths of the Journal Explanations of symbols and shading used should appear in the legend. Survival curves should be accompanied by a table giving the actual numbers of patients involved. The legends to illustrations and the footnotes to tables should contain brief but comprehensive explanations of the information contained therein. Prospective authors are strongly advised to refer to recent issues of the Journal for examples of accepted layout. A contribution towards the cost of colour reproduction is usually requested If a table or an illustration has been reproduced from a published work the original source thereof must be given in full. Permission to use published work must be obtained from the original author and the publisher before submission.

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The decimal point, not a comma, is used, e g. 5·7. A space and not a comma follows thousands and multiples thereof, e.g. 10 000. SI units (International System of Units) should be used except for the measurement of blood pressure (mmHg) Where measurements were made in non-SI units, the actual values and units should be given, with SI equivalents inserted in parentheses at appropriate points.

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## Statistics

For detailed guidance on the handling of statistical material, authors should consult *The British Journal of Surgery* 1991, **78**: 782–4 The Editors and statistical referees in evaluating a manuscript will consider the *design* of the study, the *presentation* of the data, the *analysis* of the data, and the *interpretation* of the results.

### Design

Authors should set out clearly the objectives of the study, should identify the primary and secondary hypotheses, and should explain the rationale for the choice of sample size

### Presentation

Whenever possible a graphical presentation should be used to illustrate the main findings of a study. The use of standard deviation and standard error should be clearly distinguished The use of the '±' symbol should be avoided; these statistics should be presented in parentheses after the mean value.

### Analysis

There should be a clear description of which methods were used for which analyses, and any methods not in common usage should be supported by references Results of statistical tests should be reported by stating the value of the test statistic, the number of degrees of freedom and the $P$ value. For example, '$t = 1{\cdot}34$, 16 d.f., $P = 0{\cdot}20$' might be reported. Actual $P$ values should be reported, to two decimal places, especially when the result is not significant, rather than stating 'not significant'.

Whenever possible, the results of the primary analyses should be reported using confidence intervals instead of, or in addition to, $P$ values

### Interpretation

Statistical significance should not be confused with clinical significance. In particular, 'negative' findings should be interpreted through the use of confidence intervals

Authors should beware of placing undue emphasis on secondary analyses, especially when they were suggested by an inspection of the data.

# Editors' announcements

## Dual publication

Two cases of dual publication have recently come to the attention of the Editors, as follows:

1. Pinho M, Yoshioka K, Keighley MRB. Long term results of anorectal myectomy for chronic constipation. *Br J Surg* 1989; **76**: 1163–4.

   Pinho M, Yoshioka K, Keighley MRB. Long-term results of anorectal myectomy for chronic constipation. *Dis Colon Rectum* 1990; **33**: 795–7.

Professor Keighley has apologized for an unintentional oversight, caused in part by one of his co-authors returning to another country.

2. Bremholm Rasmussen T, Ingerslev HJ, Høstrup H. Natural history of the maldescended testis. *Horm Res* 1988; **30**: 164–6.

   Bremholm Rasmussen T, Ingerslev HJ, Høstrup H. Bilateral spontaneous descent of the testis after the age of 10: subsequent effects on fertility. *Br J Surg* 1988; **75**: 820–3.

Dr Bremholm Rasmussen has not replied to our request for an explanation.

A third case was narrowly averted when the corresponding author received one set of proofs from *The British Journal of Surgery* and another from *The Lancet* in short succession He then discovered that his co-author (who had again returned abroad) had sent the manuscript to *The Lancet* without informing him.

In the opinion of the Editors, dual publication is a deplorable practice. It is a waste of time, money and precious editorial space, and it is a potential source of confusion for those who wish to examine the literature in a particular field. We appreciate that authors who update a clinical series or expand a set of experiments may wish to submit a paper that includes previously published material. In these circumstances the earlier work should be cited and its extent made clear, so that the Editors, the Referees and the readership at large can appreciate the amount of new data contained in the submission.

In the two cases listed above the data were virtually identical in each paper, likewise the discussion. The onus of avoiding dual publication rests firmly with the authors. Those who infringe these simple rules may find that any subsequent manuscripts are rejected.

## Instructions to authors

The Editors have revised the Instructions to Authors, which appear in their new format at the front of this issue of the Journal. We have taken this action to clarify the requirements for authors, particularly in relation to the statistical analysis of their data, and also to emphasize the particular requirements for different types of submission

There are several points emphasized in these revised Instructions which are designed to reduce delays in the handling of manuscripts. In future, manuscripts will be inspected at the time of submission. Where a manuscript fails to meet the requirements for layout, consent, and submission by all authors, the Editorial Office will request the author to submit a revised manuscript before any further editorial consideration.

It will be helpful to the Editorial Office if authors specify under which category the manuscript is submitted (original article, review, short note, case report or surgical workshop).

The Instructions to Authors have been revised in order to assist authors in the preparation of manuscripts. Careful attention to detail should reduce the need for later revisions and should therefore both ease the task of the Editors and reduce delay in the publication of worthwhile material.

**R. C. N. Williamson**
**J. R. Farndon**
**J. A. Murie**
**C. D. Johnson**

Br. J. Surg. 1992, Vol. 79, January, 4–5

# Cholecystectomy and gallbladder conservation

Cholecystectomy has been the standard operation for gallstone disease for over 100 years, regardless of whether the gallbladder is healthy or diseased. It is currently the most frequently performed elective major operation in the western world. Over 500 000 cholecystectomies are performed each year in the USA and up to 50 000 in the UK and Ireland. After a brief flirtation with gallbladder-conserving measures such as dissolution therapy and extracorporeal shockwave lithotripsy, the introduction of laparoscopic cholecystectomy seems set to reduce the impetus to further research into procedures which conserve the gallbladder. It is argued that laparoscopic cholecystectomy is cost-effective, and it would be easy to be swept along with the tide of economic rather than physiological considerations.

The arguments in favour of gallbladder removal include: the obvious fact that most patients are relieved of their symptoms – especially if they present with biliary colic or cholecystitis; the risk of further stone formation – up to 50 per cent at 5 years if dissolution therapy is discontinued; and the remote risk of developing gallbladder carcinoma – estimated at 0·3–2 per cent of elderly patients[1]. Against this, however, are the risk of morbidity and mortality from cholecystectomy, with the mortality rate of open cholecystectomy increasing from 0·1 per cent in those aged under 50 years to almost 10 per cent in the elderly[1], and the disturbance of upper gastrointestinal physiology which follows gallbladder removal.

Up to 40 per cent of patients continue to experience symptoms after cholecystectomy, only a minimum of which are attributable to unsuccessful surgery[2]. Symptoms after cholecystectomy may include persisting pain or dyspepsia mistakenly attributed to asymptomatic gallstones, an understandable error when abdominal ultrasonography is increasingly the first investigation carried out in patients with epigastric pain. Alternatively, biliary symptoms may have been replaced by new symptoms, which have been precipitated or exacerbated by gallbladder removal.

Loss of the reservoir function of the gallbladder results in disturbance of bile metabolism and alteration in the dynamics of bile release. Bile flow into the duodenum changes, from intermittent, meal-related to continuous, and its composition also changes, becoming more damaging to gastric and oesophageal mucosa. This leads to increased duodenogastric reflux[3], which is aggravated further by the impaired function of the antropyloric motor unit that appears to result from a direct effect of bile on the duodenum[4]. Subsequent symptoms have been related to the increased incidence of gastritis (described in up to 50 per cent of patients), to alkaline duodenogastric reflux[3], and to the qualitative change in bile composition[5].

It has recently been shown that all gastro-oesophageal reflux markers increase after cholecystectomy[6]. The reason for this is unclear but neural and hormonal mechanisms are proposed. Stuart *et al.*[7] have shown an inverse relationship between gallbladder distension pressure and lower oesophageal sphincter pressure, suggesting a neural link. Bile bathing the antrum has been shown to stimulate gastric acid secretion[8]. Sandler *et al.* have identified tachykinins in high concentrations in the fundus, which have a profound effect on lower oesophageal sphincter function; their release may be triggered by bile or by gastritis[9]. The bile salt pool is reduced by 50 per cent, which may result in subclinical fat malabsorption and postcholecystectomy diarrhoea which may be attributed to bile catharsis[10]. The presence of fat in the colon is known to excite the release of gastrointestinal hormones, most notably peptide YY which affects the motility of the antrum and pylorus[11] and which may have an effect on the lower oesophagus. More bile is in circulation at any one time and is subject to the effects of bacterial degradation, leading to the formation of secondary bile acids which have been implicated in colonic neoplasia following cholecystectomy. Werner *et al.*[12] have shown an increased risk of carcinoma of the right side of the colon in 1,2-dimethylhydrazinamine-treated mice after cholecystectomy, while case–control studies have shown an increase in right-sided colonic tumours in women after cholecystectomy[13].

In certain circumstances preservation of the gallbladder seems particularly

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desirable: for example, in the presence of gastro-oesophageal reflux as symptoms following cholecystectomy are even more frequent in such cases; or following vagotomy and pyloroplasty or gastric resection, as postvagotomy diarrhoea may become a significant problem[14].

While laparoscopic cholecystectomy currently enjoys its deserved role in the removal of the diseased and non-functioning gallbladder, parallel developments, such as percutaneous cholecystlithotomy, the Lithotrite (Baxter Corporation, California, USA), gallstone dissolution, sphincterotomy with endoscopic stone retrieval, and improved extracorporeal shockwave lithotripsy, should be considered as therapeutic alternatives for patients with functioning gallbladders, particularly for the elderly, the less fit, and the young, who may not wish to have their gallbladder removed. It is imperative that surgeons understand the necessity of preserving the functioning gallbladder and take the lead in the development and implementation of alternative modalities of treatment. Failure to do so will be exploited by others and will lead to the relegation of the general surgeon from his role as physician who can offer the entire range of therapeutic alternatives to that of technician who is called on only for crisis management.

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Br. J. Surg. 1992, Vol. 79, January, 6-7

# Pancreas and islet transplantation

The treatment of insulin-dependent diabetes by transplantation has provoked much controversy and debate; after all, there are very few deaths nowadays from the acute metabolic complications of diabetes and subcutaneous insulin replacement allows a long and active life for most patients. Complications in the form of retinopathy, nephropathy, angiopathy and neuropathy are, however, common and the question is, can transplantation prevent them? Not only is there disagreement about whether the potential benefits from transplantation are greater than the risks, there is also no conclusive evidence that restoration of normoglycaemia will prevent these complications. This debate is likely to continue for the foreseeable future because the results of treating diabetes both by conventional subcutaneous insulin[1] and by tissue transplantation are continually improving. Nevertheless, if a transplant can safely restore metabolic normality, there is no doubt that it will be welcomed by doctors and patients alike. Advances towards this goal have been made in recent years by both transplantation of vascularized pancreas and transplantation of isolated islets of Langerhans, but how close are we to success?

Over 3200 vascularized pancreas transplants have been performed at 115 institutions since 1966. As a result of improved donor and patient selection, immunosuppressive therapy, and operative technique, the 30-month patient and graft survival rates for transplants performed since 1988 are 90 and 65 per cent respectively[2]. A measure of the improvement can be judged from the corresponding figures for the period 1966–1977, which were respectively 38 and 5 per cent. The best results are obtained if the pancreatic exocrine secretions are drained into the recipient's bladder via a cuff of donor duodenum and if the pancreas transplant is performed at the same time as a kidney transplant. Although there have been 212 transplants in diabetic patients who have received the pancreas alone, it is disappointing to note that graft survival is worse in this group. However, as the bladder drainage technique becomes more widely adopted the results of solitary pancreas transplantation are expected to improve; this has already happened in some centres[3].

Although a technically successful pancreas transplant may render the recipient normoglycaemic, the procedure carries a significant morbidity rate[4] and a small but definite mortality rate[4]. The effects on diabetic complications are not fully established. Current evidence does, however, suggest that pancreas transplantation can prevent the progression of diabetic nephropathy in a simultaneously transplanted kidney, and that somatic and perhaps also autonomic neuropathy can be halted or reversed. The effect on retinopathy on the other hand has been disappointing, although one study does report a protective effect if the transplant is performed early in the course of the disease[5]. The most definite benefit from the addition of a pancreas to a kidney transplant is an improved quality of life; there are now a number of studies which confirm this[4,6].

Who should perform and who should receive a vascularized pancreas transplant? The answer to the former question is surgeons in institutions whose results are similar to those reported by the International Pancreas Transplant Registry; the answer to the latter question remains uncertain, although diabetic patients with end-stage renal failure who are receiving a pancreas in addition to a kidney can expect an improved quality of life, improved diabetic neuropathy, and less diabetic nephropathy in the transplanted kidney. The role for solitary pancreas transplantation is even less clear; a recent diagnostic and therapeutic technology assessment[7] concluded that a majority of American physicians feel that the benefits of solitary pancreas transplantation are unproven, and that the risks of immunosuppressive therapy are a major limitation to the procedure which should probably be limited to patients receiving a simultaneous kidney transplant.

Although many issues in the field of pancreas transplantation are contentious there is general agreement that the operation is unlikely to be useful for young adults or children who have recently developed diabetes, because it is impossible to predict whether the surgical and immunosuppressive risks of the procedure will be greater than the risks posed by the disease itself. This is particularly important when one considers that roughly 50 per cent of diabetic patients will not develop any *serious* long-term complication. With this limitation in mind there has been a great deal of interest in an alternative approach, namely islet transplantation.

The theoretical advantages that islet transplantation offers over whole pancreas

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transplantation are that it is a minor procedure (the islets are infused into the portal vein) and that islets can be pretreated before transplantation to reduce their immunogenicity. If successful, this could reduce or obviate the need for immunosuppression by making the recipient tolerant to the transplant. A major problem in humans has been the purification of large numbers of viable, sterile islets. This has finally been achieved by the intraductal injection of collagenase, controlled gentle mechanical disruption of the pancreas[8], and large-scale density gradient centrifugation[9]. These improvements have allowed clinical trials to be renewed. Although a number of human islet transplants had been performed before 1988 the tissue used for these procedures was poorly purified, and islet viability was poorly documented. Since 1988 a total of 39 type 1 diabetic patients have received adult islet allografts and six have achieved a period of insulin independence. The patient with the longest surviving graft has been insulin-independent for 20 months at the time of writing[10]. Most of these diabetic recipients have received their islet transplant simultaneously with, or after, a kidney transplant. Although the islets for most of these patients have been infused into the portal vein at laparotomy, or via the umbilical vein, the two recent islet transplants at the Leicester Royal Infirmary have been administered via a percutaneous transhepatic route. With one exception all of these successful islet transplants have been performed with islets from more than one donor pancreas.

In conclusion, although the results of vascularized pancreas transplantation have greatly improved, the procedure is likely to remain restricted to a small subset of the diabetic population. Human islet transplantation is in its infancy and many problems remain to be resolved, but it does have the potential through islet immunomodulation to reach patients who have not yet developed diabetic complications, and perhaps thereby to prevent them. A start has been made and we can begin to investigate the safety and efficacy of the procedure, but only time will tell whether immunomodulated human islet transplants can evade rejection and whether they will prevent the long-term sequelae of diabetes.

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**Review**

Br. J. Surg. 1992, Vol. 79, January, 8–20

# Surgical palliation for pancreatic cancer: developments during the past two decades

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*Improvements in pancreatic imaging over the past 20 years have revolutionized the preoperative diagnosis and assessment of resectability in patients with suspected pancreatic cancer. This review highlights the resultant trends in the surgical treatment of ductal carcinoma of the pancreas, comparing series reported between 1981 and 1990 with those from the previous decade. Small but worthwhile gains have been achieved both in overall resection rate and in the survival rate from such resections. Nevertheless, 80 per cent or more of affected patients are still unsuitable for resection because of the extent of their disease. Laparotomy retains a crucial role in the management of carcinoma of the pancreatic head, although percutaneous and endoscopic stents provide a useful alternative for palliation of malignant obstructive jaundice in elderly patients or those with carcinomatosis. Operation provides the chance to confirm the nature and full extent of the tumour, to circumvent duodenal obstruction and to abolish pain, besides relieving jaundice without the need for tubes (with their potential to block). By contrast, operative treatment generally has much less to offer in patients with carcinoma of the pancreatic body, unless diagnosis and irresectability remain in doubt. In combination, radiotherapy and 5-fluorouracil may achieve more as adjuncts to palliative surgery than either agent alone. The increasing safety of pancreaticoduodenectomy raises the possibility of palliative resection in younger patients with limited but incurable disease.*

In 1836, Mondiere described the gross characteristics of carcinoma of the exocrine pancreas[1]. Over the past 40 years its incidence has doubled in Western Europe, has trebled in the USA and has more than quadrupled in Japan[2,3]. Although many sophisticated investigations are now available for diagnosis, fewer than 20 per cent of patients with pancreatic cancer are suitable for possible curative resection[4,5]. These statistics underline the crucial importance of good palliative treatment for this disease.

This review will start by considering the extent of the problem of pancreatic cancer (at different sites) in terms of resectability, mortality and survival rates. The preoperative assessment and operative determination of resectability are then discussed, since these are essential for a rational choice between palliation and attempted cure. Methods for relieving jaundice, gastric outlet obstruction and pain are reviewed in detail. Lastly, we consider the role of adjuvant therapy and the possible indications for palliative resection in managing this difficult disease. The review is limited to the common ductal carcinoma of the pancreas and excludes endocrine, cystic and ampullary tumours, which carry a much better prognosis.

## The extent of the problem

### *Resectability*

Operative trends in the treatment of pancreatic cancer during the past 20 years are shown in *Tables 1* and *2*, which summarize the procedures undertaken in a total of 37 series from the English-speaking literature. Before 1980, the mean resectability rate of pancreatic cancer was 10 per cent. The figure has improved to an overall 15 per cent during the past decade, and in some centres the resectability rate now approaches 20 per cent. The explanation could be either earlier diagnosis or selected patterns of referral. Like resection, palliative surgical bypass has become rather more frequent, rising from 45 per cent (of all patients with pancreatic cancer) between 1971 and 1980 to 49 per cent between 1981 and 1990; indeed, since 1989, 57 per cent of patients with pancreatic cancer have received some form of operative bypass. As a desirable corollary, fewer patients are now undergoing laparotomy alone, the figure falling from 28 to 22 per cent since 1980. Presumably the decline in 'diagnostic' laparotomy reflects the technological advances in pancreatic imaging, notably percutaneous fine-needle aspiration cytology[5], the combination of endoscopic pancreatography and cytology[43], rapid-sequence (dynamic) computed tomography (CT)[44,45] and improved techniques of visceral angiography[46]. The development of non-operative techniques for the relief of jaundice since 1980 has contributed to the fall in the number of patients receiving laparotomy alone and also to the number considered unsuitable for any surgical intervention (from 17 to 12 per cent). In a few centres biliary endoprostheses have become first-line treatment for patients whose cancer is deemed irresectable on imaging[40,47–49], but we still adopt an operative policy towards carcinoma of the pancreatic head (as opposed to carcinoma of the body or tail in anicteric patients).

### *Operative mortality*

The trend towards active surgical treatment (whether resection or surgical bypass) during the past two decades has been

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**Table 1** *Types of treatment for patients with pancreatic ductal carcinoma during 1971–80*

| Reference | Year | Total no. of patients* | Resection | Surgical bypass | Laparotomy alone | No definitive treatment† |
|---|---|---|---|---|---|---|
| Feduska *et al.*[6] | 1971 | 101 | 16 (16) | 60 (59) | 22 (22) | 3 (3) |
| Pope and Fish[7] | 1971 | 188 | 10 (5) | 101 (54) | 49 (26) | 28 (15) |
| Aston and Longmire[8] | 1973 | 149 | 39 (26) | 67 (45) | 26 (17) | 17 (11) |
| Najera and White[9] | 1973 | 166 | 3 (2) | 49 (30) | 89 (54) | 25 (15) |
| Richards and Sosin[10] | 1973 | 222 | 31 (14) | 97 (44) | 58 (26) | 36 (16) |
| Collure *et al.*[11] | 1974 | 109 | 2 (2) | 61 (56) | 18 (17) | 28 (26) |
| Douglass and Holyoke[12] | 1974 | 81 | 10 (12) | 49 (60) | – | 22 (27) |
| Hermreck *et al.*[13] | 1974 | 348 | 51 (15) | 172 (49) | 125 (36) | – |
| Hertzberg[14] | 1974 | 270 | 12 (4) | 148 (55) | 86 (32) | 24 (9) |
| Shapiro[15] | 1975 | 297 | 24 (8) | 24 (8) | 114 (38) | 135 (45) |
| Webster[16] | 1975 | 92 | 9 (10) | 54 (59) | – | 29 (32) |
| Andersson and Bergdahl[17] | 1976 | 138 | 4 (3) | 87 (63) | 41 (30) | 6 (4) |
| Brooks and Culebras[18] | 1976 | 101 | 19 (19) | 35 (35) | 25 (25) | 22 (22) |
| Hines and Burns[19] | 1976 | 129 | 22 (17) | 75 (58) | 22 (17) | 10 (8) |
| Coutsoftides *et al.*[20] | 1977 | 329 | 27 (8) | 125 (38) | 119 (36) | 58 (18) |
| Gursel *et al*[21] | 1977 | 108 | 20 (19) | 51 (47) | 26 (24) | 11 (10) |
| Bergstrand *et al.*[22] | 1978 | 469 | 44 (9) | 240 (51) | 113 (24) | 72 (15) |
| Knight *et al.*[23] | 1978 | 421 | 21 (5) | 155 (37) | 134 (32) | 111 (26) |
| Forrest and Longmire[24] | 1979 | 232 | 62 (27) | 103 (44) | 67 (29) | – |
| Reed *et al.*[25] | 1979 | 207 | 10 (5) | 101 (49) | 28 (14) | 68 (33) |
| Total | | 4157 | 436 (10) | 1854 (45) | 1162 (28) | 705 (17) |

Values in parentheses are percentages *All patients with the diagnosis of pancreatic ductal adenocarcinoma, †patients received no treatment or only palliative chemotherapy or radiotherapy. Note: non-operative biliary decompression was not undertaken in any of these series

**Table 2** *Types of treatment for patients with pancreatic ductal carcinoma during 1981–90*

| Reference | Year | Total no. of patients* | Resection | Surgical bypass | Laparotomy alone | Non-operative biliary decompression | No definitive treatment† |
|---|---|---|---|---|---|---|---|
| Brooks *et al.*[26] | 1981 | 111 | 18 (16) | 53 (48) | 21 (19) | – | 19 (17) |
| Herter *et al.*[27] | 1982 | 363 | 82 (23) | 152 (42) | 129 (36) | – | – |
| Meinke *et al.*[28] | 1983 | 449 | 57 (13) | 238 (53) | – | – | 154 (34) |
| Kummerle and Ruckert[29] | 1984 | 782 | 174 (22) | 322 (41) | 218 (28) | – | 68 (9) |
| Morrow *et al.*[30] | 1984 | 228 | 39 (17) | 76 (33) | 80 (35) | – | 33 (14) |
| Rosenberg *et al.*[31] | 1985 | 461 | 24 (5) | 207 (45) | 134 (29) | – | 96 (21) |
| Trede[32] | 1985 | 435 | 59 (14) | 216 (50) | 78 (18) | – | 82 (19) |
| Matsuno and Sato[33] | 1986 | 272 | 45 (17) | 105 (39) | 84 (31) | 25 (9) | 13 (5) |
| Ubhi and Doran[34] | 1986 | 98 | 1 (1) | 82 (84) | 15 (15) | – | – |
| Dunn[35] | 1987 | 238 | 22 (9) | 99 (42) | 69 (29) | – | 48 (20) |
| Gudjonsson[36] | 1987 | 196 | 8 (4) | 97 (49) | 54 (28) | – | 37 (19) |
| Funovics *et al.*[37] | 1989 | 783 | 137 (17) | 420 (54) | 226 (29) | – | – |
| Jacobs *et al.*[38] | 1989 | 80 | 8 (10) | 58 (73) | 14 (18) | – | – |
| Michelassi *et al.*[39] | 1989 | 549 | 79 (14) | 399 (73) | – | – | 71 (13) |
| Hyoty and Nordback[40] | 1990 | 54 | 4 (7) | 36 (67) | – | 5 (9) | 9 (17) |
| Proctor and Mauro[41] | 1990 | 211 | 41 (19) | 70 (33) | 22 (10) | 42 (20) | 36 (17) |
| Singh *et al.*[42] | 1990 | 340 | 61 (18) | 158 (46) | 71 (21) | 15 (4) | 35 (10) |
| Total | | 5650 | 859 (15)‡ | 2788 (49)‡ | 1215 (22) | 87 (10) | 701 (12) |

Values in parentheses are percentages. *All patients with the diagnosis of pancreatic ductal adenocarcinoma; †patients received no treatment or only palliative chemotherapy or radiotherapy; ‡normal test comparing two independent proportions, $P = 0.0001$ *versus* series reported between 1971 and 1980 (*Table 1*)

accompanied by a fall in operative mortality rates (*Tables 3* and *4*). The mean mortality rate of pancreatic resection for cancer has dropped from 17 to 9 per cent and for palliative surgical procedures from 17 to 14 per cent. The emergence of specialist pancreatic surgeons may explain this improvement, at least for pancreatectomy. Trede and colleagues in Germany have recently reported pancreaticoduodenectomy in 118 patients without a single hospital death[56]. Nor is age necessarily a bar to successful surgery: Kairaluoma *et al.* from Finland reported a 10 per cent mortality rate after pancreatectomy (one

**Table 3** *Operative mortality rate and mean survival period following resection, surgical bypass and laparotomy alone. Collective review of articles published between 1971 and 1980*

| | | | Resection | | | Surgical bypass | | | Laparotomy | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Reference | Year | Total no. of patients* | No of patients | Operative mortality rate (%) | Mean survival (months) | No. of patients | Operative mortality rate (%) | Mean survival (months) | No. of patients | Operative mortality rate (%) | Mean survival (months) |
| Feduska *et al* [6] | 1971 | 98 | 16 | 7 (44) | 16·9 | 60 | 20 (33) | 5·9 | 22 | 9 (41) | 3·6 |
| Pope and Fish[7] | 1971 | 160 | 10 | 2 (20) | 21·0 | 101 | 24 (24) | 10·5 | 49 | 16 (33) | 8·4 |
| Aston and Longmire[8] | 1973 | 132 | 39 | 4 (10) | 15·4 | 67 | 10 (15) | 5·2 | 26 | 9 (35) | – |
| Najera and White[9] | 1973 | 141 | 3 | 0 (0) | 10·5 | 49 | – | 7·5 | 89 | – | – |
| Collure *et al.*[11] | 1974 | 81 | 2 | 0 (0) | 7·0 | 61 | – | 6·0 | 18 | – | 3·8 |
| Hermreck *et al* [13] | 1974 | 348 | 51 | 14 (27) | 11·4 | 172 | 41 (24) | 5·0 | 125 | 64 (51) | 1·8 |
| Hertzberg[14] | 1974 | 181 | 12 | 1 (8) | 17·0 | 148 | 19 (13) | 6·8 | 21 | 9 (43) | 1·6 |
| Shapiro[15] | 1975 | 162 | 24 | 0 (0) | 10·1 | 24 | 1 (4) | 8·6 | 114 | – | – |
| Andersson and Bergdahl[17] | 1976 | 132 | 4 | 1 (25) | 27·0 | 87 | 17 (20) | 5·5 | 41 | 15 (37) | 4·3 |
| Brooks and Culebras[18] | 1976 | 79 | 19 | 2 (11) | 23·0 | 35 | 5 (14) | 5·6 | 25 | – | 3·3 |
| Hines and Burns[19] | 1976 | 119 | 22 | – | – | 75 | 16 (21) | 8·0 | 22 | 9 (41) | 3·0 |
| Coutsoftides *et al.*[20] | 1977 | 271 | 27 | 5 (19) | 15·0 | 125 | 15 (12) | 7·4 | 119 | 40 (34) | 5·8 |
| Gursel *et al.*[21] | 1977 | 97 | 20 | 3 (15) | 17·5 | 51 | 9 (18) | 5·8 | 26 | 9 (35) | 4·0 |
| Bergstrand *et al* [22] | 1978 | 397 | 44 | 11 (25) | 12·8 | 240 | 43 (18) | 5·3 | 113 | 41 (36) | 2·4 |
| Knight *et al.*[23] | 1978 | 310 | 21 | 3 (14) | 16·0 | 155 | 34 (22) | 6·7 | 134 | 33 (25) | 3·5 |
| Forrest and Longmire[24] | 1979 | 232 | 62 | 8 (13) | 16·4 | 103 | 21 (20) | 5·6 | 67 | 29 (43) | 3·6 |
| Reed *et al.*[25] | 1979 | 139 | 10 | 3 (30) | 23·0 | 101 | 10 (10) | 9·4 | 28 | 2 (7) | 6·0 |
| Total | | 3079 | 386 | 64 (17) | 12·7 | 1654 | 285 (17) | 5·4 | 1039 | 285 (36) | 2·6 |

Percentage mortality rates are given in parentheses. * Total number of patients with pancreatic adenocarcinoma undergoing operation

**Table 4** *Operative mortality rate and mean survival period following resection, surgical bypass and laparotomy alone Collective review of articles published between 1981 and 1990*

| | | | Resection | | | Surgical bypass | | | Laparotomy | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Reference | Year | Total no of patients* | No. of patients | Operative mortality rate (%) | Mean survival (months) | No. of patients | Operative mortality rate (%) | Mean survival (months) | No. of patients | Operative mortality rate (%) | Mean survival (months) |
| Brooks *et al.*[26] | 1981 | 90 | 18 | – | – | 51 | 12 (24) | 5·5 | 21 | – | – |
| Herter *et al*[27] | 1982 | 363 | 82 | 16 (20) | 10·6 | 152 | 16 (11) | 6·0 | 129 | 12 (9) | 2·0 |
| Morrow *et al.*[30] | 1984 | 195 | 39 | 7 (18) | 18·0 | 76 | 9 (12) | 4·0 | 80 | 12 (15) | 4·0 |
| Rosenberg *et al*[31] | 1985 | 365 | 24 | 4 (17) | 24·6 | 207 | 34 (16) | 6·3 | 134 | 39 (29) | 2·9 |
| Matsuno and Sato[33] | 1986 | 234 | 45 | 3 (7) | 22·0 | 105 | 16 (15) | 5·0 | 84 | 9 (11) | 4·7 |
| Sonnenfeld *et al*[50] | 1986 | 38 | – | – | – | 38 | 10 (26) | 4·7 | – | – | – |
| Tsuchiya *et al*[51] | 1986 | 103 | 103 | 4 (4) | 17·9 | – | – | – | – | – | – |
| Ubhi and Doran[34] | 1986 | 98 | 1 | – | – | 82 | 21 (26) | 6·7 | 15 | – | – |
| Dunn[35] | 1987 | 190 | 22 | 3 (14) | 18·3 | 99 | 17 (17) | 7·6 | 69 | 21 (30) | 3·8 |
| Jacobs *et al*[38] | 1989 | 80 | 8 | – | – | 58 | 6 (10) | 8·0 | 14 | 1 (7) | 7·0 |
| Kairaluoma *et al*[52] | 1989 | 42 | 42 | 3 (7) | 16·3 | – | – | – | – | – | – |
| McGrath *et al*[53] | 1989 | 52 | – | – | – | 52 | 0 (0) | 7·0 | – | – | – |
| Griffin *et al.*[54] | 1990 | 36 | 36 | 0 (0) | 11·5 | – | – | – | – | – | – |
| Kahn *et al.*[55] | 1990 | 92 | – | – | – | 66 | 4 (6) | 11·3 | 26 | 2 (8) | 3·7 |
| Singh *et al.*[42] | 1990 | 290 | 61 | 3 (5) | 19·9 | 158 | 12 (8) | 7·3 | 71 | – | 2·4 |
| Total | | 2268 | 481 | 43 (9)† | 17·0§ | 1144 | 157 (14)‡ | 6·6§ | 643 | 96 (18) | 3·1 |

Percentage mortality rates are given in parentheses * Total number of patients with pancreatic adenocarcinoma undergoing operation Normal test comparing two independent proportions. † $P = 0{\cdot}0005$, ‡ $P = 0{\cdot}008$, § not significant *versus* series reported between 1971 and 1980 (*Table 3*) total, 15 proximal, four distal and one local resection) in 21 elderly patients (aged over 70 years) with cancer of the pancreas or periampullary region[57]. The Mayo Clinic recently published a similar experience, with a 9 per cent mortality rate following resection in a series of 42 patients with pancreatic cancer over the age of 70 years[58] Interestingly, the mortality rate of resection is now less than that of palliative bypass, presumably because those with less advanced disease are selected for resection. The welcome fall in the mortality rate of palliative surgery may be due in part to the availability of non-operative alternatives for relieving jaundice in those for whom age, infirmity or extensive disease makes any operation dangerous.

*Survival after operation*

Long-term results of surgical treatment for pancreatic cancer have also improved during the past 10 years. The mean survival time following pancreatic resection increased from 12 7 months between 1971 and 1980 to 17·0 months between 1981 and 1990. Earlier diagnosis may have played a part in this improvement. In California the diagnosis of pancreatic cancer was made 1–2 months sooner during the 1980s than it had been in the 1970s[42]. Better adjuvant (or synchronous) chemotherapy and radiotherapy may also be helping to extend survival. These changes have discredited Crile's concept (introduced in 1970) that surgical bypass is the most appropriate procedure for pancreatic cancer even if resectable and that it is associated with a longer survival period than resectional surgery[59] All articles reviewed since 1971 clearly show a longer survival time after pancreatic resection than after palliative bypass (*Tables 3* and *4*), despite the fact that many resectional operations are labelled later as non-curative. Bypass itself has been attended by a slight increase in subsequent survival time during the past decade. This finding may be due to the fact that patients with very advanced cancer are now likely to be treated by non-operative means such as endoprosthetic stenting of the biliary tract, leaving more favourable cases for surgical bypass. Since the overall mortality rate of surgical bypass is slightly less than that of laparotomy alone and the mean survival time is approximately double (6·6 *versus* 3·1 months), patients who are scheduled for exploratory laparotomy should receive some form of operative bypass if they have actual or potential obstruction of the biliary tree or duodenum.

*The site of the cancer*

Although the overall outcome of treatment for pancreatic cancer seems to be improving, this statement is true only for cancer of the pancreatic head. For cancer of the body and tail, the situation has remained dismal over the past 20 years. In 1973 Richards and Sosin[10] reported 70 patients with cancer of the body or tail of the pancreas Fifty patients underwent laparotomy, the remainder with advanced disease receiving symptomatic treatment. Among these 50, resection (i.e. distal pancreatectomy) could be carried out only in four (8 per cent), three patients (6 per cent) had palliative operations, including two gastrojejunostomies and one cholecystjejunostomy, leaving 43 who simply had a diagnostic laparotomy. Mean survival thereafter was 13·6 months (resection), 6·3 months (bypass) and 5·7 months (laparotomy alone). Another series from the early 1970s gave a 90 per cent incidence of liver metastasis and a 70 per cent incidence of regional lymph node involvement in 13 patients with cancer of the body and tail compared with 50 and 45 per cent, respectively, in 35 patients with cancer of the head[11]. By 1986 little had changed. Among 272 Japanese patients with carcinoma of the pancreas[33], 100 had tumours of the body or tail and only seven of these were treated by resection (six distal, one total). Palliative bypass was undertaken in 17 patients, leaving 70 with laparotomy alone and six with other treatment such as external biliary drainage. More than 60 per cent of the patients already had distant metastases The mean survival time was 8 4 months after resection but only 4 1 months after palliative bypass. The message is clear: ductal cancers distal to the head of the pancreas are virtually incurable and lead to death within a short space of time Unfortunately, the early diagnosis of such lesions remains elusive because of the vague symptoms they cause and the consequent delay in seeking medical advice.

## Assessment of resectability

*Preoperative assessment*

Since pancreatectomy is mainly of benefit in patients with localized disease, the aim of preoperative evaluation should be not only to assess the resectability of the primary tumour but also to search for metastases. The extent of the cancer can sometimes be gauged on clinical grounds. Back pain, which is present in about a quarter of patients with cancer of the pancreatic head, is an ominous symptom; in one series 29 of 33 such tumours were irresectable[10] Likewise, back pain occurred in 56 per cent of those patients with cancer of the body or tail, and none of these had resectable tumours. When data from 393 patients with pancreatic cancer were analysed to relate prognosis to clinical presentation, 46 per cent of those with irresectable but localized tumours and 47 per cent of those with advanced disease had back pain, while only 5 per cent of those with resectable tumours had this symptom[60]. Physical signs generally inconsistent with a resectable tumour include cervical adenopathy, ascites, a rectal 'shelf' and an umbilical nodule.

Many imaging studies are now available for preoperative evaluation of patients with pancreatic carcinoma. Ultrasonography and CT are the first-line investigations to diagnose and localize the primary tumour, to detect metastatic lesions and subsequently to guide biopsy for cytological and/or histological verification. Among 56 patients with pancreatic cancer who were potential surgical candidates, CT predicted resectability with a sensitivity of 75 per cent and a positive predictive value of 38 per cent, using the absence of local extension or distant metastases as the criteria[61] Irresectability was predicted with a sensitivity of 72 per cent and a positive predictive value of 93 per cent. Thus, CT was better at predicting irresectability than resectability, especially when hepatic or other distant metastases were present.

Ultrasonography can achieve a sensitivity approaching that of CT in detecting pancreatic carcinoma Also, in one series, irresectability of the tumour was correctly predicted by showing involvement of the major blood vessels in 12 of 51 patients. but it was missed in another four[62]. Evidence of advanced disease was obtained by identifying liver metastases in 16 of 19 patients and lymphadenopathy in 16 of 21 patients. By contrast, resectability was indicated with much less accuracy: only seven of 19 'resectable' lesions were successfully removed Overlying bowel gas, obesity and the relative inaccessibility of the organ can hamper the examination The advent of endoscopic ultrasonography (EUS) may improve matters. Tio and Tytgat[63] used EUS to predict tumour resectability in 14 patients with pancreatic cancer. EUS accurately predicted resectability in seven of eight patients and suggested irresectability in five of six, because of deep infiltration of the tumour around major blood vessels and adjacent organs. In a Japanese study of 42 patients with pancreatic cancer and eight with chronic pancreatitis[64], EUS detected all the tumours, even those of less than 20 mm in diameter. Among 12 patients with small cancers (<30 mm), malignant invasion of the portal vein was correctly diagnosed in all but one case. Unfortunately, with larger tumours it was difficult to evaluate the portal or superior mesenteric veins because of echoic reduction by the tumour. A prospective study from the Cleveland Clinic did not show quite such excellent results[65]. Although cancer of the pancreas was recognized in nine of ten cases, there were two false-positive diagnoses in patients with cholangiocarcinoma. All correctly diagnosed tumours were more than 30 mm in diameter. Technical difficulties (i.e. ruptured balloon, inability to place the transducer in the duodenum) limited the success of the examination in 24 per cent of cases, and the authors could not discover any specific findings that reliably differentiated pancreatic cancer from chronic pancreatitis. At present, EUS is still being developed but it may come to play an important role in the early diagnosis of pancreatic carcinoma.

In the preoperative evaluation of pancreatic cancer, visceral angiography provides two pieces of crucial information: anatomical anomalies of the blood vessels and vascular invasion by tumour. Atypical arterial patterns, notably a replaced right hepatic artery, can be anticipated in 25 per cent of patients considered for pancreatectomy, and this information is useful during mobilization of the pancreatic head[66]. The most reliable angiographic sign of irresectability is clear-cut invasion or obstruction of the portal or superior mesenteric vein, especially when collaterals show that this finding is not an artifact. Arterial encasement is a less reliable criterion, although total occlusion of one of the major arteries nearly always denotes irresectability[67].

Despite conventional imaging, Warshaw and colleagues found that nearly half the patients who came to laparotomy with apparently localized pancreatic cancers had unsuspected intra-abdominal metastases[68]. They therefore evaluated laparoscopy as a further staging modality in 40 pancreatic cancers (25 proximal, 15 distal). Laparoscopic assessment was accurate in 93 per cent overall and altered the treatment plan in 35 per cent (usually by avoiding open operation). Cuschieri undertook laparoscopy in 73 patients with pancreatic cancer as an immediate prelude to laparotomy in 51 cases[69]. Forty-two of 47 patients were accurately staged as having incurable lesions, but only four of nine judged to be resectable at laparoscopy had truly resectable tumours at laparotomy. Although most hepatic deposits visualized by laparoscopy had been detected by preoperative imaging, peritoneal and omental deposits were identified only endoscopically.

Warshaw *et al.* prospectively evaluated four different imaging techniques for detecting resectability in 88 patients with pancreatic and ampullary tumours[70]. CT was 92 per cent accurate for predicting irresectability but only 56 per cent sensitive; by contrast, it was only 45 per cent accurate in predicting resectability. Magnetic resonance imaging had no advantage over CT. Visceral angiography was 95 per cent accurate at predicting irresectability but only 66 per cent sensitive. Laparoscopy detected liver or peritoneal seedlings in 22 of 23 patients and was 100 per cent accurate concerning their absence. When CT, angiography and laparoscopy were combined, 51 of 57 irresectable tumours (89 per cent) and 28 of 31 resectable tumours (90 per cent) were correctly identified.

In our opinion, no single preoperative test is sufficiently reliable to determine the resectability of every pancreatic carcinoma. Although the combination of imaging studies improves the accuracy rate, laparotomy remains the final arbiter

*Intraoperative assessment*

Surgical exploration of the abdomen and especially a trial dissection to separate the superior mesenteric and portal veins from the overlying neck of pancreas are the crucial steps in deciding between a resectional and a palliative approach. A tumour deemed irresectable on preoperative imaging may occasionally turn out to be resectable after all. It can be difficult to differentiate between compression of the great veins and actual invasion, and Trede resected the tumour in one patient who appeared to have gross portal vein obstruction at angiography[32] Lymph node involvement can be confirmed by frozen-section examination but does not necessarily preclude resection provided the nodes can be excised *en bloc*. In a recent French study[71], surgical exploration was supplemented by operative ultrasonography to assess the resectability of 22 pancreatic lesions Operative ultrasonography proved useful in seven patients: in three the discovery of venous involvement precluded further efforts at resection, in three the absence of such involvement encouraged resection to proceed and in one demonstration of a normal splenic vein permitted spleen-preserving distal pancreatectomy. In our experience, the most reliable method for assessing resectability is a careful trial dissection of the tumour supplemented as necessary by frozen-section examination of any doubtful lesions.

Histological confirmation is crucial in all patients suspected of having malignant disease. In those with resectable tumours, evidence of malignancy and staging of the disease can best be obtained by examination of the resection specimen. In those with irresectable tumours, it is essential to confirm the existence and type of cancer by obtaining appropriate biopsies at operation, so that appropriate (but potentially toxic) treatment can be selected and the prognosis can be rationally assessed. Sampling a nodal or hepatic metastasis may be the simplest method. Otherwise, the surgeon should have no hesitation in performing direct pancreatic biopsy. Available techniques include core needle biopsy (our own preference), incision (wedge) biopsy, shave biopsy of the edge of the lesion plus fine-needle aspiration for cytology. Early experiences of intraoperative biopsy of pancreatic lesions showed an accuracy rate of 60 per cent or less. The results have progressively improved, and most large centres are now reporting accuracy rates of between 85 and 90 per cent[72,73].

Because liver hamartomas can mimic secondaries, enlarged nodes may simply be reactive and distal obstructive pancreatopathy is difficult to differentiate from the primary tumour, biopsy material should be sent for frozen-section histology. Witz and colleagues[74] examined frozen-section material obtained by wedge biopsy, transduodenal needle biopsy or fine-needle aspiration in 51 patients. Subsequent paraffin sections confirmed that the immediate diagnosis was correct in 48 cases (94 per cent), comprising 44 of cancer and four of chronic pancreatitis; false-negative results occurred in the remaining three cases. Although a higher complication rate has been noted with core needle biopsy than wedge biopsy[75], it can be difficult to determine whether complications are related to the biopsy or to the concomitant surgical procedure employed, and needle biopsy is usually preferred for 'awkward' deep-seated lesions. We agree with Cooperman's statement that 'the safest and best method is the one the surgeon is most familiar with'[76]. We regard a palliative operation that does not produce a clear-cut tissue diagnosis as a failure.

## Relief of jaundice

*Surgical biliary bypass* versus *endoprosthesis* (Table 5)

During the 1980s, percutaneous transhepatic stenting and endoscopic transpapillary stenting have become established methods for the palliation of jaundice in patients with malignant obstruction of the extrahepatic biliary tree. It is obviously attractive to avoid a major operation in those with a very limited expectation of life, but with two provisos: that the nature and irresectability of the tumour can be established beyond doubt and that subsequent quality of life is not eroded by the need for further hospital admissions.

Percutaneous transhepatic endoprostheses are associated with a lower mortality rate than surgical bypass (9 *versus* 12 per cent) and with a shorter hospital stay (14 *versus* 17 days) and lower early complication rate (16 *versus* 31 per cent). By contrast, long-term complications, especially recurrent jaundice and cholangitis, appear to be more common (28 *versus* 16 per cent). A variety of different types of endoprosthesis are now available, with large lumens ranging from 9 to 14 Fr in external diameter[48]. Stent materials include Teflon® (E.I. du Pont, Wilmington, Delaware, USA), polyethylene and Percuflex® (MediTech, Watertown, Massachusetts, USA). In most patients percutaneous transhepatic stenting is carried out in two stages. The first stage consists of placing an external–internal drainage tube (under local anaesthesia) through the liver past the malignant stricture and into the duodenum. The second stage of the procedure is carried out a couple of days later and comprises dilatation of the tract to an

**Table 5** *Comparative results between surgical bypass and endoprosthetic stents in patients with malignant obstruction of the common bile duct*

| | Surgical bypass* ($n = 1807$) | | Percutaneous stents† ($n = 490$) | | Endoscopic stents‡ ($n = 689$) | |
|---|---|---|---|---|---|---|
| | Range | Mean | Range | Mean | Range | Mean |
| 30-day mortality rate (%) | 0–31 | 12 | 6–33 | 9 | 0–20 | 14 |
| Hospital stay (days) | 9–30 | 17 | 13–18 | 14 | 3–26 | 7 |
| Success rate (%) | 75–100 | 93 | 76–100 | 92 | 82–100 | 90 |
| Early complications (%) | 6–56 | 31 | 4–67 | 16 | 8–34 | 21 |
| Late complications (%) | 5–47 | 16 | 7–38 | 28 | 13–45 | 28 |

* References 26, 27, 29–31, 34, 35, 38, 40–42, 50, 53, 77–86, † References 83, 84, 87–91, ‡ References 40, 47, 49, 82, 84–86, 90, 92

appropriate size and insertion of the endoprosthesis. The advent of self-expanding metallic endoprostheses has opened a new era of percutaneous stenting. The Wallstent endoprosthesis (Medinvent SA, Lausanne, Switzerland) is made of a closely woven mesh of stainless steel and is introduced percutaneously through a 7 Fr catheter. When the stent is released it achieves a maximal diameter of 10 mm. Adam and his colleagues have reported their successful experience using this metallic stent in 41 patients with malignant obstructive jaundice, including 12 with pancreatic cancer[87] The short-term minor complication rate was 12 per cent, and no procedure-related death occurred. The large internal diameter of this stent provides long-term patency, thereby reducing complications. The major disadvantages of this type of stent are its high cost and the difficulty in removing or replacing it if it blocks. However, another stent can be placed above or below if tumour overgrowth occurs.

A variety of endoscopic biliary endoprostheses of different shapes, materials and size is now available: single pigtail, double pigtail or straight with side flaps. They are 7–12 Fr in outer diameter and vary considerably in length. Stents are made from Teflon, polyethylene or polyurethane. In general, a 10–12-cm prosthesis is used for distal biliary obstruction, while a longer, 15–20 cm, tube is preferred for bifurcation lesions. Leung and colleagues[93] conducted a simple *in vitro* study to assess the performance of different types of endoprosthesis. A straight configuration was shown to provide the best flow rate, and there was no difference between straight tubes of different materials. Flow rates were not affected by adding large side-holes or retention flaps, but tapering or the formation of a pigtail reduced the flow by as much as 50 per cent. In general, the larger and straighter the prosthesis, the better the flow[48,92,93]. Moreover, straight stents are easier to insert. Although papillotomy is not compulsory, most endoscopists use it to facilitate passage of larger prostheses and to provide access for subsequent manipulation or exchange of the stents. At present, endoscopic biliary stenting has a similar overall success rate (82–100 per cent) to surgical bypass and percutaneous stenting, and offers the shortest hospital stay (7 *versus* 14–17 days). Again, the benefit of a lower rate of early complications is balanced by an increased rate of late complications, compared with surgical bypass.

In some patients stenting can be difficult. Placement of a large-bore endoprosthesis by the percutaneous transhepatic route is painful and requires a large tract through the hepatic parenchyma, while the presence of duodenal diverticula, angulation of the duct or proximal strictures may preclude successful insertion of an endoscopic prosthesis. In such cases a combined percutaneous and endoscopic approach can be employed for stent insertion. A percutaneous guidewire is manipulated through the obstructing lesion from above and retrieved through an endoscope. The prosthesis is then fed through the endoscope over the guidewire and across the biliary stricture. Robertson and colleagues[94] used this combined method in 14 patients in whom a biliary stent could not be placed endoscopically. The success rate was 97 per cent, and there were no early complications Two other groups[95,96] had a similar experience and found that prostheses inserted by the combined route were easily replaced when they occluded.

The major late complication leading to recurrent jaundice or cholangitis is clogging of the endoprosthesis, which occurs in 20–30 per cent of cases (whether placed from above or below)[48,88,89]. Speer and co-workers[97] studied the basic mechanism of clogging to find ways to prevent it. Light and electron microscopy have shown that the material blocking the lumen is composed of a matrix of bacterial cells and their fibrillar anionic extracellular products. Crystals of calcium bilirubinate, calcium palmitate and cholesterol are embedded within this matrix The presence of bacterial cells attaching to the stent surface by a fibrillar matrix suggests that the initial event in stent clogging is the development of an adherent bacterial biofilm. Clogging usually occurs after a mean of about 5 months. The use of a polymer with an intrinsic antibacterial action or an antibiotic coating on the surface of the prosthesis may reduce bacterial adhesion and stent clogging. If clogging occurs, the tube should be replaced as soon as possible[48].

Non-operative placement of endoprostheses is gaining in popularity. Most published reports are restricted to patients who are unsuitable for any surgical treatment. Although the number of patients submitted to laparotomy alone should continue to decline, therefore, the percentage of patients receiving surgical bypass has increased from 45 to 49 per cent while laparotomy alone declined from 28 to 22 per cent over the past decade (*Tables 1* and *2*). Operative decompression of the biliary tract remains the most effective method for 'long-term' palliation of jaundice in patients with irresectable pancreatic cancer.

### *Preoperative biliary drainage*

Previous studies have shown that operations in deeply jaundiced patients are associated with operative mortality rates of 15–25 per cent and morbidity rates of 40–60 per cent[98–101], hence the interest in preoperative biliary decompression[99–106]. Unfortunately, any potential gains in terms of a lower complication rate were masked by the complications of the procedure itself when percutaneous transhepatic biliary drainage was employed. Thus, in the randomized study of Pitt *et al.*[105], the 30-day mortality rate was marginally higher in those with preoperative percutaneous drainage than in undrained patients (8·1 *versus* 5·3 per cent), and total hospital stay was extended (31·4 *versus* 23·1 days) When a major resection is planned, preliminary biliary decompression may be considered (and the endoscopic route is probably the best), but in palliative surgery it seems unnecessary.

### *Types of surgical biliary bypass* (Table 6)

The most common biliary–enteric bypass carried out for irresectable pancreatic cancer is still cholecystjejunostomy, although in our opinion it is seldom the most appropriate. The relative frequency of cholecystjejunostomy has increased from 50 per cent in the 1970s to 62 per cent in the 1980s. Choledochojejunostomy, our own preference, has also increased from 7 to 22 per cent during this time. Some centres, notably the Cleveland Clinic, still prefer to use the duodenum for biliary–enteric bypass[77], but the choice of either duodenum or stomach is generally decreasing because of the potential for duodenal obstruction and bile gastritis.

**Table 6** *Operative mortality rate and mean survival period with different types of surgical biliary bypass. Collective review of articles published between 1971–80 and 1981–90*

| | 1971–80‡ | | | 1981–90§ | | |
|---|---|---|---|---|---|---|
| | Total (%)* (*n*=894) | Operative mortality rate (%) | Mean survival (months) | Total (%)* (*n*=970) | Operative mortality rate (%) | Mean survival (months) |
| Cholecystduodenostomy | 154 (17) | 16 (11) | 6·4 | 28 (3) | – | 6·0 |
| Choledochoduodenostomy | 159 (18) | 24 (18) | 7·5 | 105 (11) | 1 (2) | 7·8 |
| Cholecystjejunostomy | 450 (50) | 51 (17) | 4·7 | 598 (62) | 32 (10) | 6·7 |
| Choledochojejunostomy | 61 (7) | 29 (34) | 5·7 | 209 (22) | 11 (7) | 9·2 |
| Cholecystgastrostomy | 11 (1) | – | – | 8 (1) | – | – |
| Others† | 59 (7) | – | – | 22 (2) | – | – |

Values in parentheses are percentages. * Percentage of each procedure for surgical bypass, † including cholecystostomy, U or T tube external drainage; ‡ References 6, 10, 11, 14, 16, 17, 19, 21, 22, 25, 107; § References 26, 31, 34, 40, 50, 53, 77, 78, 81, 108, 109

**Table 7** *Initial success rate (in relieving jaundice) and incidence of recurrent jaundice or cholangitis following cholecystenterostomy and choledochoenterostomy in patients with irresectable pancreatic cancer. Collective review of articles published between 1971 and 1990*

| | Initial success rate (%) | | Recurrent jaundice or cholangitis (%) | |
|---|---|---|---|---|
| | Range | Mean | Range | Mean |
| Cholecystenterostomy | 50–97 | 89 | 1·5–64·0 | 20 |
| Choledochoenterostomy | 93–100 | 97 | 7·3–16·6 | 8 |

References 10, 14, 26, 34, 77, 107–109

Use of the distended gallbladder on the biliary side of the anastomosis is certainly the simplest option, and it is associated with a shorter operative time than using the common bile duct. The operative mortality rate of cholecystjejunostomy has decreased from 17 per cent before 1980 to 10 per cent since that time. Choledochojejunostomy used to carry a much higher operative mortality rate (34 per cent during 1971–80), but this is no longer the case (7 per cent since 1981). The greater technical difficulty of choledochojejunostomy may be balanced by the modern trend to reserve cholecystjejunostomy for patients with advanced cancer who are expected to survive for only a few weeks. In a well matched study by Rosemurgy *et al.*[108], 22 patients underwent cholecystjejunostomy and 15 patients underwent choledochojejunostomy. The operative mortality rate was 23 per cent for gallbladder–enteric bypass and only 7 per cent for common duct–enteric anastomosis; the morbidity rates were similar (59 and 53 per cent, respectively) and still much too high. In a meta-analysis of eight articles comparing these two procedures (*Table 7*), cholecystenterostomy carries an 89 per cent success rate, while that of choledochoenterostomy is 97 per cent. An important finding that emerges from this review is the 20 per cent incidence of recurrent jaundice or cholangitis following gallbladder bypass, compared with only 8 per cent after common duct bypass. In general, choledochoenterostomy should therefore be preferred in patients with a reasonable expectation of survival. If the gallbladder is selected for the anastomosis, one must ensure that the cystic duct is patent and that it enters the common duct at least 2–3 cm above the tumour mass. Intraoperative cholangiography (through the gallbladder) may establish these facts. Mere observation is fallible, since the cystic duct may merge with the common duct high up, only to join it much lower down.

Is the additional anastomosis required to create a defunctioned (Roux) loop justifiable in the palliation of pancreatic cancer? An experimental study in dogs has clearly demonstrated that Roux-en-Y cholecystjejunostomy and choledochojejunostomy were associated with a lower incidence of cholangitis than simple anastomosis to a functioning loop of jejunum[110]. In clinical practice, when a biliary–enteric bypass is performed for benign biliary obstruction and long survival is anticipated, a Roux-en-Y jejunal anastomosis is considered superior to a simple loop. In patients with irresectable pancreatic cancer, however, Sarr and Cameron found no advantage for Roux-en-Y anastomosis over a simple loop in a review of 1100 patients[111]. Brooks *et al.* confirmed no superiority for the one procedure over the other[26], and recently Potts *et al.* reported a similar incidence of biliary sepsis following each technique of anastomosis[77]. The infrequency of ascending cholangitis when functioning jejunum is used is probably due to the short survival of these patients. Although Roux-en-Y anastomosis takes a little longer to perform, we still use it routinely, partly because we employ the top of the same Roux loop for concomitant gastroenterostomy.

## Relief of duodenal obstruction

*Gastroenterostomy: routine* versus *selective* (Table 8)

Nausea and vomiting are presenting symptoms in 30–45 per cent of patients with pancreatic cancer, although actual gastric outflow obstruction occurs in only 5 per cent at the time of diagnosis[17]. As the tumour enlarges, there is a further risk of duodenal invasion and obstruction. Tumours in the head of the gland normally obstruct the second part of the duodenum, whereas lesions of the body and tail may involve the fourth part.

A review of more than 1600 cases of pancreatic cancer from 15 articles published between 1973 and 1990 (*Table 8*) shows that the mortality rate of biliary bypass is not increased by adding gastrojejunostomy (12 *versus* 14 per cent). The mean survival time for patients without initial gastroenterostomy is slightly longer than for those with initial gastroenterostomy (7·4 *versus* 6·7 months), probably because those with more advanced disease are chosen for the extra procedure. Seventeen per cent of patients (range 4–44 per cent) who undergo biliary bypass alone will develop duodenal obstruction at a mean of 8·6 months later and require subsequent gastric bypass. This is a very substantial figure when one considers that this is a selected group of patients who were considered at the time of operation to be unlikely to develop duodenal obstruction. The mortality rate of this second operation varies between 6 and 100 per cent (mean 22 per cent), and mean survival thereafter is only 3·0 months.

Delayed gastric emptying (DGE) occurs after operation in 20 per cent (range 6–29 per cent) of patients undergoing gastroenterostomy at the time of biliary bypass[38,42,78,114,115]. Doberneck and Berndt[114] found that DGE complicated recovery in seven of 43 patients (16 per cent) who had no preoperative evidence of duodenal obstruction and in eight of 14 patients (57 per cent) who did. Two of 12 patients (17 per cent) with gastroenterostomy proximal to the

**Table 8** *Operative mortality rate and mean survival period of patients with and without initial gastrojejunostomy at the time of biliary bypass. Collective review of articles published between 1971 and 1990*

| | | | Those with initial gastrojejunostomy | | | Those without initial gastrojejunostomy | | | Those going on to gastrojejunostomy later | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Reference | Year | Total no of patients* | No. of patients | Operative mortality rate (%) | Mean survival (months) | No of patients | Operative mortality rate (%) | Mean survival (months) | No. of patients | %† | Operative mortality rate (%) | Mean interval‡ (months) | Mean survival§ (months) |
| Richards and Sosin[10] | 1973 | 91 | 21 | 4 (19) | 6·5 | 70 | 14 (20) | 5·5 | 19 of 56 | 34 | 2 (11) | 7·1 | 3·6 |
| Collure *et al.*[11] | 1974 | 49 | 24 | – | – | 25 | – | – | 5 of 25 | 20 | – | 14·0 | 3·0 |
| Hertzberg[14] | 1974 | 148 | 5 | 0 (0) | 6·8 | 143 | 18 (13) | 6·8 | 7 of 125 | 6 | – | – | – |
| Reed *et al*[25] | 1979 | 87 | 30 | 2 (7) | 7·7 | 57 | 6 (11) | 9·4 | 6 of 47 | 13 | – | – | – |
| Brooks *et al*[26] | 1981 | 41 | 5 | – | 9·8 | 36 | – | 7·8 | 6 of 36 | 17 | 2 (33) | 11·9 | 1·6 |
| Meinke *et al*[28] | 1983 | 216 | 111 | 16 (14) | – | 105 | 15 (14) | – | 29 of 90 | 32 | – | 5·0 | – |
| Lee[112] | 1984 | 111 | 64 | 7 (11) | – | 47 | 8 (17) | – | 3 of 39 | 8 | – | 4·0 | – |
| Schantz *et al.*[78] | 1984 | 103 | 46 | 7 (15) | 8·4 | 57 | 8 (14) | 8·8 | 6 of 49 | 12 | 1 (17) | 8·0 | – |
| Rosenberg *et al.*[31] | 1985 | 187 | 47 | 10 (21) | 5·2 | 140 | 19 (14) | 7·1 | 18 of 121 | 15 | 1 (6) | 9·1 | 2·5 |
| Ubhi and Doran[34] | 1986 | 78 | 42 | 6 (14) | 6·7 | 36 | 11 (31) | 6·7 | 11 of 25 | 44 | – | – | – |
| La Ferla and Murray[113] | 1987 | 100 | 14 | 2 (14) | – | 86 | 24 (28) | – | 8 of 62 | 13 | – | 5·4 | 2·5 |
| Jacobs *et al*[38] | 1989 | 58 | 17 | 3 (18) | 4·2 | 41 | 3 (7) | 9·4 | 14 of 38 | 37 | 7 (50) | 9·8 | 3·9 |
| McGrath *et al*[53] | 1989 | 52 | 47 | 0 (0) | 7·0 | 5 | 0 (0) | 7·0 | 2 of 5 | 40 | 2 (100) | – | – |
| Holbrooks *et al*[81] | 1990 | 165 | 37 | 10 (27) | 7·8 | 128 | 18 (14) | 7·0 | 11 of 110 | 10 | 2 (18) | – | – |
| Potts *et al.*[77] | 1990 | 122 | 56 | 0 (0) | 6·0 | 66 | 3 (5) | 8·0 | 7 of 63 | 11 | – | – | – |
| Total | | 1608 | 566 | 67 (12) | 6·7 | 1042 | 147 (14) | 7·4 | 152 of 891 | 17 | 17 (22) | 8·6 | 3·0 |

Values in parentheses are percentage mortality rates *Total number of patients undergoing biliary bypass procedure; †percentage of those surviving initial biliary bypass and undergoing subsequent gastrojejunostomy; ‡mean interval from biliary to gastric drainage; §mean survival time after second operation (gastrojejunostomy) biliary–enteric anastomosis had DGE compared with six of 22 patients (27 per cent) with gastrojejunostomy distal to the biliary bypass. Jacobs *et al.*[38] described a 29 per cent incidence of DGE among patients who underwent both biliary and gastric bypass, while no DGE occurred in the group with biliary bypass alone. Barkin *et al.*[116] showed that nine of 15 patients with pancreatic cancer (60 per cent) without duodenal obstruction or electrolyte imbalance had gastric emptying curves more than two standard deviations below normal mean values. Nausea and/or vomiting was present in three of nine with abnormal gastric emptying but in none of those with a normal test. The mechanism of DGE is still uncertain. Some patients may have partial obstruction at or close to the stoma, whereas others with extensive nodal secondaries may have a degree of autonomic gastric denervation. Fortunately, the condition usually settles spontaneously after varying periods of nasogastric intubation.

Upper gastrointestinal bleeding occurs in 0–17 per cent of patients with double bypass[10,38,78,79,115] and 2–6 per cent of those with biliary bypass alone[38,79]. Sarr *et al.* reported bleeding from stomal ulcer in three of 100 patients[117]; others may have duodenogastric reflux and alkaline gastritis. Vagotomy is probably not justified because of the low incidence of stomal ulcer, and it may further complicate DGE after operation. Routine use of histamine ($H_2$) receptor antagonists seems a wise precaution after operation.

We favour gastroenterostomy at the time of initial biliary bypass in most patients with irresectable cancer of the pancreatic head because of: (1) the high incidence of subsequent duodenal obstruction if this step is omitted; (2) the fact that it does not increase the mortality rate; and (3) the substantial risk of postoperative death if a second operation is required for duodenal obstruction. Increased morbidity in terms of DGE and gastrointestinal bleeding can usually be treated by conservative means. However, there is room for judgement in individual cases. If the tumour is arising from the neck of the pancreas or beyond, or if distant spread makes survival unlikely beyond a few weeks, then the addition of gastroenterostomy may be superfluous.

## Relief of pancreatic pain

Pain is a presenting symptom in 70–90 per cent of patients with pancreatic cancer, although it is often mild and will settle after appropriate bypass operation or stenting. More severe pain, especially back pain, is characteristic of carcinoma of the body and tail[118] and invasive lesions of the head. Pain seems to be related to the stage of the disease. Singh *et al.* found that 65 per cent of those undergoing palliative bypass had moderate-to-severe pain compared with more than 85 per cent of those who were unsuitable for any operation[42,119].

Palliation of pain in patients with advanced pancreatic carcinoma can be as difficult as it is worthwhile, but an attempt should certainly be made at laparotomy. Pancreatic duct decompression over a T tube into the stomach or jejunum has been tried with some benefit but without dramatic pain relief[120]. It is worth considering in irresectable cancers that are confined to the head and are causing marked obstruction of the pancreatic duct. Ductal dilatation may be suspected on preoperative imaging (notably CT) and confirmed by palpation at laparotomy and/or ambigrade intraoperative ductography[121]. Although biliary or gastrointestinal obstruction may contribute to the pain of pancreatic cancer, fewer than 10 per cent of patients are relieved by appropriate bypass, and even then the pain invariably recurs within a few weeks or months of the operation[42,119]. In one recent case pain was successfully relieved by endoscopic stenting of the dilated pancreatic duct in a patient with irresectable cancer of the pancreatic head, although the stent required frequent replacement owing to obstruction by thick proteinaceous material[122]. Endoscopic stenting of a dilated pancreatic duct merits further evaluation.

Peroperative chemical ablation of the coeliac ganglia is a more attractive option for treating the severe pain of pancreatic cancer. Gardner and Solomou[123] reported their experience of chemical splanchnicectomy using 40 ml 5 per cent phenol in almond oil. Thirty of 37 patients (81 per cent) who had suffered pain before operation and survived for 10 days or more after operation experienced pain relief, and in 26 (70 per cent) this relief persisted until death. Less favourable results were seen in another series of 30 patients receiving 20–30 ml 50 per cent ethanol: pain was abolished or significantly reduced in 19 (63 per cent) but was unchanged in the remaining 11 (37 per cent). Because peroperative chemical splanchnicectomy is simple, effective and safe, it can be recommended whenever pain is a prominent presenting feature. If the intraoperative procedure fails or pain recurs, a percutaneous coeliac block can be carried out at a later date.

Pancreatic cancer pain can also be palliated by radiation, usually external beam therapy. External beam radiation should certainly be considered in patients whose pain recurs after intraoperative chemical splanchnicectomy. In one series[124], 66 patients with irresectable pancreatic carcinoma received radical radiotherapy, 48 with precision high-dose (PHD) external radiation and 18 with an iodine-125 implant; the dose of PHD radiation was 50 Gy with a cone down to the tumour to 65 Gy. Twenty-three of the 48 patients had presented with pain, and of these 61 per cent had complete relief and 30 per cent had partial relief. Low-dose radiation in 33 patients gave less favourable results. Intraoperative radiotherapy is an effective but much more cumbersome alternative, Matsuno and Sato[33] achieved excellent palliation of pain in four of 18 patients and good palliation in another eight.

## Adjuvant therapy following palliative surgery

Pancreatic cancer is generally regarded as a radioresistant tumour with low susceptibility to anticancer drugs, but promising results are sometimes reported. In one small study of 11 patients undergoing surgical bypass and four having laparotomy alone, external beam radiation at a dose of 55–60 Gy prolonged survival time from 3·5 to 8 months[125]. Unfortunately others have not confirmed the value of adjuvant radiotherapy[126,127]. Combining radiation modalities, for example interstitial or intraoperative radiation plus external beam photon irradiation, may possibly improve results, but controlled studies are awaited.

In 1958 Heidelberger *et al.* demonstrated that regression of certain transplanted animal tumours was enhanced by the addition of 5-fluorouracil (5-FU)[128], and others have confirmed the benefit of adding 5-FU to radiation treatment in experimental models[129,130]. In a randomized clinical study involving 64 patients with pancreatic cancer[131], radiotherapy alone (at a moderate dose of 35–37·5 Gy over 4 weeks) was compared with radiotherapy plus 5-FU (by rapid injection at a total dose of 45 mg/kg given over the first 3 days of radiotherapy). The combined therapy showed a clear survival advantage (10·4 *versus* 6·3 months, $P<0·05$). The Gastrointestinal Tumor Study Group confirmed these results in 227 patients with locally advanced pancreatic cancer, comparing high-dose radiation alone (60 Gy) with a similar dose (40–60 Gy) plus 5-FU; combined therapy prolonged survival time from 23 weeks to 40–42 weeks[126]. Recently, Kahn and colleagues[55] have compared the results in 36 patients with surgical bypass alone and 30 with synchronous chemotherapy and irradiation. Treatment comprised ten courses of 5-FU (750 mg/m$^2$ intravenously over 8 h) followed 8 h later by radiation with 4 Gy repeated every 4 days to the total dose of 40 Gy. Synchronous therapy extended mean survival time from 8·9 to 13·5 months and relieved pain in nearly 80 per cent of patients. Toxicity from synchronous therapy was minimal, no antiemetic drugs were required, and there were no cases of myelosuppression.

The benefit of adjuvant therapy in irresectable pancreatic cancer remains questionable. Does the modest extension of life justify the potential side-effects and the added burden of extra hospital visits? Only further prospective studies can resolve the issue, yet they seem fully justified by the limitations of current surgical treatment

## Palliative resection

Until recently the substantial risks of death and complications after pancreaticoduodenectomy precluded the use of this operation unless there was a chance of curing the patient thereby This policy must now be reviewed in the light of mortality rates of 5–10 per cent in several centres, especially since 30–60 per cent of pancreaticoduodenectomies are subsequently labelled non-curative (i.e. some tumour is left behind)[52,132,133]. Kairaluoma and colleagues in Finland[52] resected cancers of the pancreatic head in 39 patients with an overall 8 per cent mortality rate Subsequent microscopic evaluation of the resected specimens confirmed that the resection had been 'curative' in only 23 (59 per cent) The mean survival time among the 16 patients with palliative resection was 10 months, which exceeds that of palliative bypass procedures (mean 6·6 months, *Table 4*). A similar report from the Netherlands[133] included 23 palliative resections for cancer of the pancreatic head with a survival time ranging from 2 to 29 months. For cancer of the tail of pancreas, distal pancreatectomy may sometimes be considered for a resectable tumour even in the presence of liver metastases. When the primary is in the body of pancreas, however (as opposed to the tail), involvement of the superior mesenteric vessels nearly always precludes even palliative resection. Trede[32] concluded from his own experience that palliative pancreatectomy can be justified if the operative mortality rate is low enough, ideally 3 per cent or less. Few can achieve a comparable level of safety at present, yet further improvements in adjuvant therapy could justify palliative resection in younger patients with a limited tumour burden.

## Conclusions

Although the resectability rate has increased during the past decade, pancreatic cancer remains an appalling disease. Only palliative therapies can be offered to the majority of sufferers, most of whom are dead within a year. Non-operative biliary decompression by transhepatic or transampullary endoprosthesis has become an established means for relieving jaundice and is of particular value in poor-risk surgical candidates, including those with very advanced disease. Like many surgeons, we favour operative palliation in most patients with irresectable pancreatic head cancer, reserving biliary endoprostheses for elderly or high-risk patients without evidence of duodenal obstruction who are expected to survive for no more than a few weeks. Laparotomy provides the opportunity to obtain definitive histology, confirm irresectability beyond any doubt, provide permanent biliary and duodenal bypass, and address the problem of intractable pain all at one time. However, we are much more reluctant to operate on those with cancer of the body or tail of pancreas, because such patients usually die from disseminated malignancy before the tumour obstructs the bile duct or duodenum sufficiently to cause jaundice and vomiting. We try to confirm irresectability (by CT and angiography), obtain a tissue diagnosis (by percutaneous guided biopsy) and then treat the pain (by means of radiotherapy, with or without 5-FU). As for surgical palliation of pancreatic cancer, we prefer Roux-en-Y choledochojejunostomy for biliary bypass and usually add a prophylactic gastrojejunostomy. In those with troublesome pain we routinely perform peroperative chemical splanchnicectomy with 50 per cent alcohol. To date we have only occasionally undertaken palliative resection of the pancreatic head in those with limited distant spread but feel there may be a role for this procedure in a few selected cases Lastly, if there is carcinoma at or close to the resection margin, we mark the area with metal clips and refer the patient for adjuvant therapy after operation

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**Review**

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# Lasers in surgery

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*In January 1991 the winter meeting of the Surgical Research Society was held at St. Bartholomew's Hospital and the Institute of Education, London. During the meeting a symposium was held entitled 'Shedding light on lasers'. Speakers addressed the general principles of lasers, laser–tissue interactions and the applications of lasers in gastroenterology and in vascular disease. This was followed by an open discussion of the current indications, complications and outcome, together with future possible applications for lasers in medicine.*

Laser technology is advancing rapidly, and as more powerful and refined devices become available the potential to treat a wide variety of conditions continues to expand. The term 'laser' is an acronym for 'light amplification by stimulated emission of radiation', a concept originally aired by Einstein in 1917[1] The first laser was built by Maiman in 1960[2], using a ruby crystal and an intense light source. Light in an ordinary household lightbulb is produced by the process of spontaneous emission. The electric current passing through the lamp causes electrons in the atoms of the filament to move transiently into a higher orbit. As they spontaneously decay to their ground state, light energy is released in the form of a photon.

In a laser, atoms with electrons in high energy orbits are subjected to further energy stimulation by photons of a specific wavelength to cause the release of identical photons, so-called stimulated emission. This reaction, occurring at the speed of light, can be contained within a chamber called a resonator This amplifies the process to produce an intense concentration of photons which, when transmitted from the resonator, form the laser beam. The basic physical nature of the beam is that of coherent light, comprising photons of a specific wavelength that are in phase in both space and time.

## Laser types

The wavelength emitted is governed by the active medium within the resonator which can be a solid, a liquid or a gas. The wavelengths produced can vary from the ultraviolet (<400 nm), through the visible spectrum (400–700 nm), and into the infrared (>700 nm). Lasers currently used in medicine and their wavelengths are shown in *Figure 1*. Excimer (EXCIted diMER) lasers[3] produce a range of ultraviolet wavelengths using dimer complexes of inert and halogen gases such as xenon chloride and argon fluoride They are predominantly used in ophthalmology but are undergoing trials in atheroma ablation. The argon laser[4] produces two wavelengths at the blue-green end of the spectrum (488/514 nm), using argon gas as the active medium. Its main use is in dermatology and ophthalmology.

The helium-neon laser, wavelength 633 nm, is a lower-power device used in measurement and alignment in radiotherapy and as a lecture-theatre pointer. The neodymium YAG laser[5] utilizes a crystal of yttrium–aluminium–garnet which contains a small proportion of ions of the rare-earth metal neodymium It produces a near infrared wavelength (1064 nm) which is invisible to the human eye. The carbon dioxide laser[6] uses a mixture of carbon dioxide and nitrogen gas to produce far infrared radiation (wavelength 10 600 nm) Both the carbon dioxide and the NdYAG lasers have been widely used in medicine as cutting and coagulating tools Dye lasers[7] use liquid solutions of certain complex organic dyes and are 'tunable', producing a wide variety of wavelengths across the visible spectrum. There are two fundamental varieties of laser energy output · the 'continuous wave', in which a constant laser beam is produced, and 'pulsed output' in which the energy is emitted in short high-energy bursts.

## Laser–tissue interaction

The nature of the interaction between lasers and tissue depends upon the output wavelength and energy, and upon the light absorption properties of the target tissue. At low powers of the order of tens of milliwatts per square centimetre, chemical reactions can be induced within tissues, a process fundamental to 'photodynamic therapy' used in the treatment of some tumours by producing a 'photochemical' effect Most current applications of lasers in medicine use much higher powers (10–1000 W/cm$^2$) and rely upon the conversion of continuous-wave laser light energy into heat in the tissue, producing 'photothermal' effects of coagulation and vaporization Pulsed laser energy can locally confine and modify thermal effects in tissues and produce disruptive 'photomechanical' shockwaves with peak pulse powers of the order of $10^5$ W. At these high intensities laser plasmas are produced comprising ionized molecules. At ultraviolet wavelengths (250–400 nm), produced by the Excimer family of lasers, individual photons can contain sufficient energy to disrupt intermolecular bonds, termed a 'photoablative' effect[8]

When light energy impinges on tissues it can be reflected, scattered or absorbed. Absorption usually predominates, although scattering is greater at some wavelengths (e g. near-infrared). Absorption is wavelength-dependent and is enhanced in the visible spectrum by tissue pigments such as haemoglobin and melanin By careful selection of the wavelength, enhanced absorption in the target tissue can be achieved. For example, to produce thrombosis in the microvasculature of 'port-wine' arteriovenous malformations, the argon laser (488/514 nm) is used to target haemoglobin. In vascular surgery, the 480 nm wavelength of the pulsed dye laser is absorbed by the yellow carotenoid pigment in atheroma

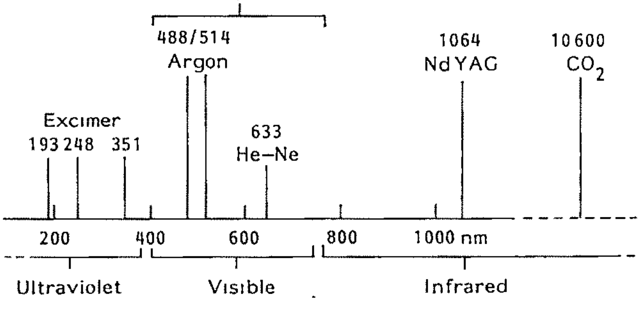

**Figure 1** *Medical lasers and their wavelengths*

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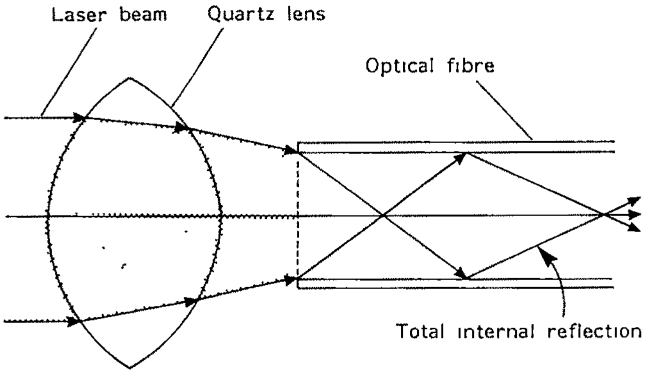

**Figure 2** *Coupling of laser energy into an optical fibre*

## Delivery devices

Delivery of laser energy for most medical applications is via flexible quartz optical fibres, usually coupled to the laser beam by a quartz lens. Fibres comprise a central core of high-quality glass coated with a thin layer of glass at a slightly lower refractive index (*Figure 2*). Light is transmitted along the fibre by total internal reflection. Fibres typically range in diameter from 0·1 to 1 0 mm, according to the laser power and flexibility required. Visible and near-infrared wavelength laser energy is easily conducted along standard optical fibres with negligible power loss Unmodified 'bare' fibres are suitable for delivery of energy where there is no direct physical contact with the target, but a range of devices has been devised with which to modify the tip for 'contact' laser applications. The most frequently used are a variety of ovoid and pointed tips made from industrial sapphire[9] which diffuse the laser beam to varying degrees. For use with the pulsed dye laser in vascular recanalization, a ball-tipped fibre has been produced by controlled fusion of the fibre itself[10].

Ultraviolet (Excimer) and far-infrared ($CO_2$) wavelengths are not easily conducted along standard fibres. The clinical application of the carbon dioxide laser utilizes a series of articulated mirrors to overcome this problem, but this precludes its use in flexible endoscopic procedures. The longer Excimer wavelengths (e g. 351 nm) are moderately well conducted by multifibre catheters.

## Specific laser applications in surgery

### *Oesophagogastric cancer*

Carcinomas of the oesophagus and gastric cardia are increasingly common and are usually advanced at presentation. Curative surgical resection or radiotherapy is seldom possible[11–14] Dysphagia is usually prominent and necessitates effective palliation, with morbidity kept to a minimum. Endoscopic intubation is now widely used[15,16] and has a relatively low associated mortality rate but a high morbidity rate[17–19] Endoscopic laser ablation in malignant dysphagia offers an alternative or adjuvant form of palliative therapy in this condition, for which life expectancy is only 4–5 months[20–33].

The currently favoured technique of laser recanalization of oesophageal lesions is employed under light sedation, using the continuous-wave NdYAG laser conducted via a flexible optical fibre passed through the channel of a gastroscope. A typical laser power of 60–70 W is applied in short 1–2-s bursts, with the fibre positioned 5–10 mm from the tumour target Tumour ablation is usually performed from the distal end of the tumour, working proximally. The laser energy produces both coagulation of tissue and vaporization, the proportion of which depends largely on the laser power. If the lesion is totally obstructing the lumen, a dilatation is initially performed. If dilatation proves impossible, an initial channel may be created with the laser by the usual non-contact technique. Some groups favour a contact technique, using a fibre capped with an industrial sapphire tip at relatively low laser powers (15 W)[32,33]

Laser vaporization is best applied to exophytic lesions protruding into the lumen, and is less satisfactory for flat tumours and those in which extrinsic compression is a major component[33]. Both squamous tumours of the oesophagus and adenocarcinomas of the gastric cardia can be treated, and it is also possible to treat recurrent tumour after previous surgery[29]. Very proximal tumours of the cervical oesophagus are sometimes excluded because of access problems and the high risk of aspiration, but effective alternative therapies are lacking Tumours greater than 6 cm in length may prove difficult to palliate because of rapid recurrence of dysphagia[29]. Improvement in dysphagia occurs in 80–85 per cent of patients after one to three treatments These are typically performed 72 h apart to allow oedema to settle and sloughing to occur Some groups electively retreat patients at 4–6-week intervals, while others delay until symptoms recur. Better palliation seems to occur with the former method. Barr *et al.* have conducted a controlled prospective study of laser vaporization *versus* laser treatment and intubation, and found similar rates of symptom relief, although complication rates were significantly lower (10 *versus* 40 per cent) using the laser alone[31].

The complications of laser therapy are primarily perforation and oesophagobronchial fistulation Perforation occurs in approximately 5 per cent of cases, leading to a pneumomediastinum or pneumoperitoneum. Conservative management is usually effective. Fistula formation into the bronchial tree is a well recognized complication of oesophageal cancer which may be both caused and unmasked by laser debulking. The treatment, as in spontaneous cases, is intubation Failure of palliation with laser treatment occurs in a further 5 per cent of cases and is usually due to long circumferential tumours and extrinsic compression. Again, intubation may then be helpful.

### *Colorectal cancer*

At diagnosis approximately one-third of patients with rectosigmoid cancer are incurable due to advanced locoregional and distant disease. The aim of palliation in this group is to improve the local problems of bleeding, discharge, tenesmus and obstruction, with minimal morbidity and mortality rates. Palliative surgical resection carries a morbidity rate of up to 50 per cent and a mortality rate of up to 17 per cent, often with a permanent colostomy and prolonged recovery in a short survival period[34–36]

Laser resection of rectosigmoid tumours using the continuous-wave NdYAG laser offers an effective means of palliation that can be performed on a day-case or short-stay basis[37–47]. Full bowel preparation is not necessary · a phosphate enema before the treatment is usually adequate Via a flexible sigmoidoscope an optical fibre is used to deliver 60–80 W of NdYAG laser power to coagulate and vaporize the tumour surface, beginning at its proximal extent and working distally The eyepiece of the endoscope is modified with infrared-absorbing glass to protect the operator. Symptomatic improvement usually occurs after one to three treatments in more than 80 per cent of patients. For stenotic tumours, an initial balloon dilatation may be used, with a series of laser treatments needed to achieve effective recanalization.

Palliation is more easily achieved where tenesmus and discharge are the predominant symptoms rather than obstruction due to circumferential tumour growth. Elective retreatment every 6–8 weeks appears to offer better palliation[37,43,44] than treating only at symptom recurrence[42]. Laser therapy is not effective for pain from local pelvic wall infiltration, and failure to improve symptoms despite good tumour clearance can occur in low rectal lesions due to sphincter disturbance causing anal incontinence.

General tolerance of the procedure is good, with some mild discomfort during treatment and, initially, an increased discharge due to tumour necrosis. The incidence of complications is generally low and studies of quality of life support the use of the laser for tumour ablation[45,47]. Loizou *et al.* reported no procedure-related mortality in a series of 49 patients[43]. Perforation may occur in 5 per cent, especially when treating rectosigmoid lesions[43,44]. It is managed with a defunctioning colostomy. Fistulation, sepsis and bleeding are also reported in a small proportion of cases. For comparison, radiotherapy is useful for palliation in 50 per cent of patients with tenesmus and discharge, but a defunctioning colostomy is usually necessary and the effects are short-lived, with proctitis, delayed haemorrhage and fistulation as common complications[48–51]. Radiotherapy may, however, be of use as an adjuvant to laser palliation in cases of pelvic wall spread. Electrocoagulation has also been shown to be effective but requires anaesthesia and also carries a high risk of complications[52–54]. Cryosurgery for palliation has a similar efficacy to the laser, but desloughing and rectal discharge can continue for up to 2 weeks and considerable complication rates have been reported[55,56].

Effective primary laser ablation of small and early carcinomas has been reported[44,57]. This role of laser therapy is controversial because nodal spread will already have occurred in a proportion of 'early' tumours. The sensitivity of endoluminal rectal ultrasonography at approximately 80 per cent[58] would not identify all of these cases. Such use of the laser as a curative tool is not fully justified, except perhaps in those unfit for, or refusing, surgery

The management of rectal villous adenoma with laser ablation is a useful alternative to surgical removal or for the treatment of recurrence after surgery[28,44,59,60]. Brunetaud *et al.* have advocated the use of the less penetrating argon laser (488/514 nm)[44] to treat these more superficial lesions.

### *Photodynamic therapy for neoplasia*

Photodynamic therapy is the process of tissue destruction by an exogenous cytotoxic chemical, activated in the tissues by light. This effect was first recorded by Smetana[61] in 1938. Lasers offer a means of controlled targeting of a chemical with a specific light wavelength. Haematoporphyrin derivative and dihaematoporphyrin ether (Photofrin II) are the agents that have had most clinical use, although newer agents such as aluminium sulphonated phthalocyanine are being explored[62,63] When given intravenously, such agents are taken up by all cells and, while cleared to varying degrees from normal tissue[64,65], are preferentially retained in malignant tissue[66], especially in tumour stroma[67]. Porphyrin accumulation in tissues was demonstrated by Figge *et al.*[68] in 1948 and this work was subsequently expanded to demonstrate selective fluorescence of malignant tissue after systemic administration of haematoporphyrin[69]. On exposure to red light energy at a wavelength of 630 nm (produced by an argon-pumped dye laser or gold-vapour laser), atoms in the photosensitive molecule are excited and react with molecular oxygen producing a singlet $O^-$ This transitory radical is thought to damage blood vessel endothelium, perhaps by disruption of subcellular organelles, causing destruction of the tumour microcirculation and death of malignant cells[70–74]. The photochemical reaction is dependent on both the light dose and the concentration of the photosensitizing agent[62] Significant fibrosis is seen in some tumours, which may result from direct photothermal effects of the laser energy rather than a pure photochemical mechanism[75] The initial clinical report of photodynamic therapy was by Lipson *et al*[76] who demonstrated regression of an ulcerating breast carcinoma. Much of the subsequent work focused on bronchial[77,78], head and neck[79] and bladder cancer[80].

In the field of gastroenterology, there are now several uncontrolled series describing the endoscopic treatment of advanced and recurrent oesophageal[81–85], gastric[83–87] and colorectal[84,85,88] tumours. Tajiri *et al.*[89] have effectively treated a series of early oesophageal and gastric tumours, and the use of photodynamic therapy has recently been reported in the treatment of extrahepatic biliary carcinoma[90]. In experimental studies photodynamic therapy has been shown to ablate both pancreatic[91,92] and hepatic tumours[93,94]. Surface illumination of tumours is generally achieved with a variety of diffusion devices mounted on the end of the laser fibre. Krasner *et al.*[95,96] have used the interstitial approach, inserting laser fibres into tumours at a variety of sites to delivery energy directly. In the majority of cases photodynamic therapy can be shown to cause tumour regression, with biopsy-proven eradication in a small proportion. Local side-effects such as oedema and haemorrhage are relatively common. Skin photosensitivity for several weeks after treatment can be a particular problem.

Studies are currently assessing these methods of treatment as both primary and adjuvant therapy, using single and combinations of photosensitizing drugs[97–99] It may prove feasible to achieve more specific delivery of sensitizing agents by linking them to either monoclonal antibodies[100] or to lipoproteins in liposomes[101].

### *Arterial recanalization*

The first clinical case of laser recanalization of an occluded artery was reported by Ginsburg *et al.* in 1984[102] following 4 years of intense research interest. They used an optical fibre (0·2 mm in diameter) linked to a continuous-wave argon laser. Following this there were small prospective studies with bare fibres in the femoropopliteal segment, which showed unacceptable rates of mechanical perforation of vessels[103,104]. Hussein then devised the laser-probe or 'hot-tip' device comprising a solid metal cap crimped to an optical fibre[105] All the laser energy applied was converted to heat in the cap, which reached temperatures of the order of 500°C Conduction to the surrounding tissues produced vaporization. The resulting channel was not sufficient to sustain flow, and balloon dilatation was almost invariably used to augment the lumen, a situation that has become the norm in all subsequent modifications of these techniques Initial short-term patency results were good[106] but this has not been borne out by other groups[107–109] and may be very operator dependent. In order to allow direct interaction of the laser light with the atheroma target, sapphire-tipped optical fibres were then introduced, coupled to the continuous-wave NdYAG laser[110,111]. Prince *et al.*[112,113] showed that pulsed laser energy is capable of ablating calcified tissue, and Cross *et al.*[114,115] that, by pulsing energy, thermal damage to the tissue surrounding the vaporized area could be limited. If the laser pulse length is short compared with that of the thermal relaxation time of tissue, heat accumulation is avoided. The pulsed NdYAG laser was then introduced into the clinical sphere by Michaels *et al.*[116] and Kvasnicka *et al.*[117]. Atheroma contains a variety of pigments, the major components being of the carotenoid family. These are predominantly yellow in colour and there is selective absorption of blue-green light by atheroma in comparison with normal arterial wall[118]. The pulsed dye laser at a wavelength of 480 nm was introduced to take advantage of this differential effect and the benefits of photomechanical ablation produced by pulsed energy[119]. The fused ball-tipped fibre was introduced as a delivery device[10] because microsecond pulsing degrades sapphire tips. The Excimer pulsed ultraviolet laser was also shown to ablate tissues precisely[120], exploiting the photoablative effect described above. Its clinical application has been limited by fibre transmission problems, although multifibre catheters have partially overcome this problem[121,122]

Most groups have concentrated on lesions that would normally be considered for balloon angioplasty alone[116,121,122], while others have focused on longer lesions as an alternative to femoropopliteal bypass[123,124], treating long segments of the superficial femoral artery occluded from its origin. This latter type of lesion requires an open rather than a percutaneous access technique, but also allows attention to be given to the origin of the profunda femoris artery Generally the early results from all groups were fairly similar, although case selection varied widely. Recanalization is achieved by most systems in 70–80 per cent of short lesions (1–7 cm)[121,122] but this is similar to that which can be achieved by a guidewire alone[122] In longer lesions (8–20 cm) the laser systems achieve a slightly higher success rate[122] Calcification has proved to be a major problem, even with pulsed laser systems[121–124], and may relate to the relatively low energy densities produced by the current delivery devices, especially if multifibre catheters are used

Procedure complications such as dissection and perforation are relatively common but do not require surgical intervention, and distal embolization is rare. Restenosis and reocclusion are both common, with typical 1-year patency rates of 50 per cent[121–124]. This is similar to results obtained with balloon angioplasty alone[125–127] although, overall, lasers have been used to treat longer lesions. Undoubtedly this early clinical experience with laser systems for recanalizing peripheral arteries has proved more problematic than originally predicted As yet there is no adequate 'stand-alone' procedure, and adjuvant balloon dilatation is required to augment the luminal diameter. Studies have, however, shown that it is possible to recanalize long femoropopliteal occlusions via a proximal percutaneous approach, avoiding the need for major vascular surgery.

Further work is needed to develop reliable methods of recanalizing calcified lesions and to elucidate the causes and prevention of restenosis, which remain the major limiting factors in achieving successful long-term recanalization.

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# Bacteriology of anal fistulae

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*Anal fistulae are said to arise from cryptoglandular infection of the anal glands, which lie within the intersphincteric space. The type and virulence of the micro-organism responsible may determine whether an anal fistula develops. The microbiology of chronic anal fistulae has not been reported previously. Twenty-five consecutive anal fistulae were studied prospectively (eight intersphincteric fistulae, 12 trans-sphincteric fistulae, two suprasphincteric fistulae, one extrasphincteric fistula, one superficial fistula, one anovaginal fistula). There were 18 men and seven women, with a median age of 42 (range 22–71) years. Patients with Crohn's disease or acute anorectal suppuration were excluded. In 18 patients, 0·1 ml granulation tissue from the track of the fistula was obtained and processed within 4 h using standard microbiological techniques. Sixty-nine isolates representing at least 17 species were obtained. The predominant organisms were* Escherichia coli *(22 per cent),* Enterococcus *spp. (16 per cent) and* Bacteroides fragilis *(20 per cent). The majority of the growths were obtained only from enrichment. Bacteria from only one patient grew at a dilution of $10^3$. Granulation tissue from 25 patients was processed for mycobacterial culture, and* Mycobacterium tuberculosis *was grown from one patient. No other mycobacterium was isolated. The chronic inflammation in anal fistulae does not seem to be maintained by either excessive numbers of organisms or organisms of an unusual type.*

The bacteriology of anorectal sepsis has attracted considerable interest over the past few years. The major point of interest has been the finding that the presence of gut bacteria, as opposed to bacteria derived from skin, in the pus from anal abscesses indicates an unsuspected anal fistula[1–4]. Whether this is because tracks that communicate with the anorectum are more likely to be colonized by gut bacteria or because virulent or unusual gut organisms are important as aetiological factors in the genesis of anal fistula has never been investigated[5]. Tuberculosis is widely recognized as a rare cause of anal fistula[6], but the role of chronic infection in the maintenance of anal fistula has not been well studied.

These questions were addressed by studying the relationship between micro-organisms and non-acute anal fistulae

## Patients and methods

Material from 25 consecutive chronic anal fistulae was studied prospectively There was an initial pilot study in seven patients in which only mycobacterial cultures were grown, thereafter, curettings from a further 18 patients were cultured for a wide range of organisms including *Mycobacterium tuberculosis* Patients with acute anorectal suppuration or Crohn's disease were excluded from the study

### *Bacteriological studies (part A)*

Eighteen patients with anal fistulae admitted for surgery within the study period were included No antibiotic therapy was used in this group of patients The usual preoperative skin preparation with 1 in 30 dilution Savlon® (I.C I. Pharmaceuticals, Wilmslow, UK) was used in all cases During surgery a 0 1 ml sample of granulation tissue was obtained from the deep tissues of the fistula which were inaccessible to the earlier skin preparation. A standard sample was obtained with a curette spoon (0 1 ml capacity). Specimens were transported in 1 ml sterile thioglycolate broth and processed within 4 h

The specimen was ground in a Griffiths' tube ($10^1$ dilution) and 1 $\mu$l was transferred to 1 ml thioglycolate broth ($10^3$ dilution). One microlitre of this dilution was transferred to a further 1 ml thioglycolate broth ($10^6$ dilution) An aliquot of undiluted specimen was inoculated into 10 ml Robertson's Cooked Meat Broth (Southern Group Laboratory, London, UK) for enrichment culture Each dilution was cultured on to blood agar (aerobic and anaerobic), McConkey agar and Wilkins–Chalgren (Unipath, Basingstoke, UK) anaerobic agar using a 1 $\mu$l standard loop The Robertson's Cooked Meat Broth specimen was subcultured after 24 h incubation on to the same media

All isolates were identified by standard microbiological methods

### *Mycobacterial studies (part B)*

In 25 patients, granulation tissue was cultured for mycobacteria As much tissue as was obtainable for each patient from surgery was sent in sterile containers to the laboratory These specimens were ground and inoculated on to Lowenstein–Jensen medium (with and without pyruvate) and into Kirschner's medium (Southern Group Laboratory) Cultures were kept for 8 weeks.

## Results

Eighteen men and seven women were included in the study There were eight intersphincteric, 12 trans-sphincteric, two suprasphincteric and one each of extrasphincteric, superficial and anovaginal tracks. Of the 18 specimens cultured for bacteria, all grew gut organisms and several different species were grown from each patient, with a range of two to six species each.

Sixty-nine isolates consisting of at least 17 different species of micro-organism were obtained from part A of the study (*Table 1*). The predominant Gram-negative organism in the anaerobic group was *Bacteroides fragilis* (20 per cent) The predominant Gram-positive aerobic organisms were *Enterococcus* spp. (16 per cent). *Escherichia coli* (22 per cent) was the predominant Gram-negative aerobic organism isolated. Overall, however, there was a paucity of organisms grown Three-quarters of all isolates were grown only after incubation in enriched culture, whilst less than a quarter of isolates were obtained on culture of the neat specimen. Only one specimen grew organisms at the $10^3$ dilution and none was grown at the $10^6$ dilution.

Of the 25 specimens cultured in part B of the study, tissue from one patient grew *Mycobacterium tuberculosis.* No other mycobacterium was cultured

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**Table 1** *Bacterial isolates for 18 anal fistula specimens*

| | Isolates per 0.1 ml tissue | | | |
|---|---|---|---|---|
| | Enrichment | Neat | $10^3$ Dilution | Total |
| Aerobic and facultative bacteria | | | | |
| Gram-negative bacteria | | | | |
| *Escherichia coli* | 10 | 5 | 0 | 15 |
| *Proteus mirabilis* | 6 | 1 | 0 | 7 |
| *Morganella morganii* | 1 | 0 | 0 | 1 |
| *Klebsiella aerogenes* | 1 | 0 | 0 | 1 |
| *Enterobacter agglomerans* | 1 | 0 | 0 | 1 |
| Gram-positive bacteria | | | | |
| *Enterococcus* spp. | 9 | 2 | 0 | 11 |
| Group F streptococci | 1 | 1 | 0 | 2 |
| Group B streptococci | 1 | 0 | 0 | 1 |
| *Streptococcus viridans* | 1 | 0 | 0 | 1 |
| Coagulase-negative staphylococci | 2 | 0 | 0 | 2 |
| Diphtheroids | 3 | 0 | 0 | 3 |
| Anaerobic bacteria | | | | |
| Gram-positive bacteria | | | | |
| *Propionibacterium* spp | 2 | 0 | 0 | 2 |
| *Clostridium* spp (not *C perfringens*) | 1 | 2 | 0 | 3 |
| *Bifidobacterium* spp | 1 | 0 | 0 | 1 |
| *Peptostreptococcus* spp. | 1 | 0 | 1 | 2 |
| Gram-negative bacteria | | | | |
| *Bacteroides fragilis* group | 9 | 5 | 0 | 14 |
| 'Black pigmenting *Bacteroides*' | 2 | 0 | 0 | 2 |
| Total | 52 | 16 | 1 | 69 |

## Discussion

It is generally accepted that an anal fistula is secondary to an acute anorectal abscess The cryptoglandular theory postulates that such an abscess begins in the intermuscular space to discharge into the anal canal at the dentate line and externally on to perianal skin[7–12]. Goligher *et al.*[13] are alone in casting doubt on this theory There is no knowledge as to the mechanism of onset of an acute anorectal abscess and the factors that maintain the resulting fistula are unknown, but it is reasonable to suppose that micro-organisms play a part

A fistula might be maintained or perpetuated by the chronic presence of organisms, by an excessive number of organisms, or by strains of virulent organisms. The microbiology of acute anorectal sepsis has been well described, with bowel-derived organisms associated with the presence of a fistula[1–3]. The microbiology of anorectal fistulae is not well reported. We have shown that culture of granulation tissue from a fistula produces similar organisms to those grown from acute abscesses, that is bowel-derived organisms An excessive number of organisms was not grown and nearly all isolates could be grown only from enriched or neat bacterial cultures, showing that the populations were not large.

At first sight, this may not seem surprising; cultures from tissue yield few organisms in comparison with pus, from which large numbers of organisms can be grown. The issue becomes one of degree: in comparison, tissue excised at the time of reoperation on an infected arthroplasty, for example, will yield organisms much more readily. Given the setting of a chronic abscess, the numbers of organisms found are less than one might reasonably have expected. Virulent organisms were not found, as those grown were normal commensals of the lower gastrointestinal tract

Tuberculous fistulae may heal after appropriate anti-microbial chemotherapy without surgery[14]; fistulae at other sites often close spontaneously when there is no gross residual sepsis, no continuing underlying disease process and no distal obstruction. Given that the pus from anorectal abscess contains large numbers of organisms, it is rather surprising that the very much smaller numbers of organisms demonstrated in this study were associated with persistence of the fistula track. This study suggests that bacterial colonization by a variety of bowel organisms may occur in chronic anal fistulae

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# Management of the perineal wound following abdominoperineal resection: prospective study of three methods

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*A prospective study was made of three procedures for treating the perineal wound and presacral cavity in 102 patients undergoing abdominoperineal excision for cancer of the rectum: (1) packing of the presacral space after suture of the pelvic peritoneum; (2) suture of the pelvic peritoneum and perineal wound, leaving two drains through the perineum; and (3) no suture of the pelvic peritoneum, and primary closure of the perineal wound, leaving drains through the abdomen for physiological saline irrigation. The parameters analysed were incidence of infection, primary healing of the perineum, extraperineal complications and mean hospital stay. Primary healing of the perineum was best with method 3, and overall incidence of infection highest with method 2. There were no differences between the methods with regard to extraperineal complications. Hospital stay was shortest with method 3.*

Treatment of the perineal wound and presacral cavity after abdominoperineal resection of the rectum for cancer remains controversial. Most surgeons prefer primary closure[1–7]. Alternative managements include suturing or not of the pelvic peritoneum[5,8,9]; introduction of passive or suction drains through the abdomen or perineum[1–10]; continuous irrigation of the presacral cavity[11–14]; and methods for filling the presacral space[8,15–18].

This paper evaluates three procedures for treating the perineal wound and presacral cavity after abdominoperineal excision of the rectum for cancer: (1) the perineal wound was left open with packing; (2) both the perineal wound and pelvic peritoneum were sutured, using passive drains through the perineum; and (3) only the perineal wound was sutured, leaving drains through the abdomen for physiological saline irrigation.

## Patients and methods

This prospective, non-randomized study was carried out between January 1985 and December 1989 on 102 patients with adenocarcinoma of the rectum treated by abdominoperineal resection. Patients in whom the tumour could not be removed completely (palliative resection), those who required packing owing to opening of the rectum with faecal spill, and those with bleeding problems were excluded. Patient details in each of the study groups are shown in *Table 1*

Preoperative preparation was the same for all patients. Cleansing of the colon was performed by means of anterograde irrigation with 10 per cent mannitol, and all patients received antibiotic prophylaxis (metronidazole and tobramycin) for the first 72 h All patients underwent surgery by the same surgical team.

The perineal wound and presacral cavity were treated by three different methods.

### *Method 1 Packing of the presacral cavity (34 patients)*

After closing the pelvic peritoneum the presacral cavity was packed with dressings lubricated with petroleum jelly through the perineal opening Dressings were changed daily until the procedure could be carried out as an outpatient treatment.

### *Method 2 · Primary closure of the perineal wound with perineal drainage (34 patients)*

After primary closure of the perineum and closure of the pelvic peritoneum, two rubber drainage tubes were placed into the presacral cavity and pulled through the floor of the ischiorectal fossa on each side of the perineal wound. The tubes were removed between the fourth and seventh day after operation, or when the volume of fluid collected was less than 50 ml/day

### *Method 3 Primary closure of the perineum with abdominal drainage plus irrigation (34 patients)*

After primary closure of the perineum, the floor of the pelvis was not reperitonealized, leaving the presacral cavity open to the abdominal cavity Three rubber tubes were placed into the presacral cavity through the right and left iliac fossae. Two of the tubes (one in each iliac fossa) acted as drains and the third was used to perform continuous irrigation of the presacral cavity, with 1500 ml physiological saline over 24 h. Twelve hours later the three abdominal tubes were removed

The following parameters were studied in each patient group. First, perineal infection and primary healing of the perineum. Infection was marked by the presence of macroscopic pus at the perineum or at the opening of the perineal wound in groups 2 and 3 The incidence of infection was correlated with the stage of the tumour and the method of closure Second, extraperineal complications: surgery-related abdominal complications (intra-abdominal abscess, abdominal wound infection, intestinal obstruction) were documented. Lastly, hospital stay was recorded.

### *Statistical methods*

Comparisons were made between two variables using analysis of contingency tables by means of Pearson's $\chi^2$ test. When small numbers were compared, Fisher's exact test was used. Student's paired $t$ test was used for statistical analysis of the hospital stay.

## Results

Primary healing of the perineum was achieved in 18 patients from group 2 (53 per cent) and 29 patients from group 3 (85 per cent), with significant differences between the two groups ($P < 0{\cdot}01$).

Perineal infection was observed in 26 of the 102 patients

**Table 1** *Age and sex of the patients undergoing each of the three methods*

| | Method 1 | Method 2 | Method 3 | Total |
|---|---|---|---|---|
| Mean age (years) | 63·9<br>(33–87) | 63·3<br>(36–89) | 60·9<br>(42–87) | 62·7<br>(33–89) |
| Sex ratio (M:F) | 20:14 | 20:14 | 14:20 | 54:48 |

Values in parentheses are ranges

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**Table 2** *Perineal infection rate in relation to stage of tumour and method of treatment*

| Dukes' classification | Method 1* ($n = 34$) | Method 2† ($n = 34$) | Method 3* ($n = 34$) |
|---|---|---|---|
| A ($n = 17$)‡ | 0 of 4 | 1 of 5 | 0 of 8 |
| B ($n = 41$)§ | 2 of 7 | 7 of 15 | 2 of 19 |
| C ($n = 44$)§ | 3 of 23 | 8 of 14 | 3 of 7 |

*$P$ = n s (patients with Dukes' A tumours *versus* B *versus* C), †$P < 0·001$ (patients with Dukes' A tumours *versus* B and A *versus* C), ‡$P$ = n s (method 1 *versus* method 2 *versus* method 3), §$P < 0·05$ (method 2 *versus* method 1 and method 2 *versus* method 3). All comparisons, $\chi^2$ or Fisher's exact test

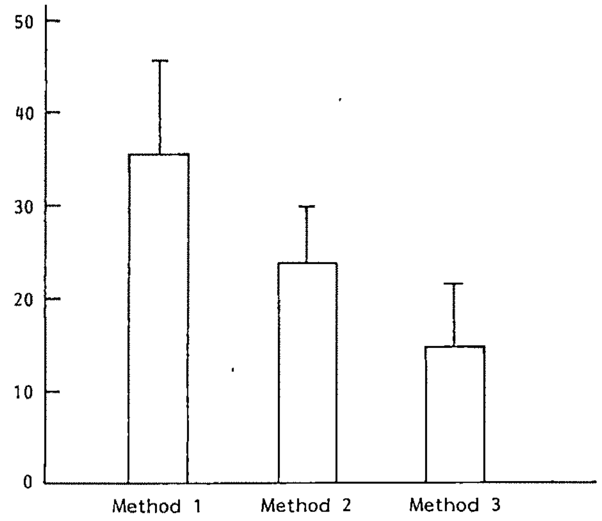

**Figure 1** *Mean(s d ) length of hospital stay with each of the three methods* P < *0·001, method 1* versus *method 2, method 1* versus *method 3 and method 2* versus *method 3 (all Student's paired* t *test)*

(25 per cent). Five of these patients were in group 1 (15 per cent), 16 were in group 2 (47 per cent) and five were in group 3 (15 per cent) Group 2 patients had significantly more infections than groups 1 and 3 ($P < 0·001$). Perineal infection occurred in one of 17 patients with Dukes' A tumours (6 per cent), in 11 of 41 patients with Dukes' B tumours (27 per cent) and in 14 of 44 patients with Dukes' C tumours (32 per cent) Rates of infection increased from those with Dukes' A to B to C tumours ($P < 0·05$). The relationship between perineal infection, tumour stage and method of treatment is shown in *Table 2*.

Extraperineal complications occurred in 23 patients One patient in group 1 had an intra-abdominal abscess. Abdominal wound infection was observed in five patients from group 1, in six from group 2 and in seven from group 3. Intestinal obstruction was more frequent in group 2 (three cases) than in group 3 (one case) and group 1 (no cases).

With method 1, the mean(s.d.) length of hospital stay was 35·7(12·2) (range 11–63) days; with method 2 it was 23·7(7·3) (range 13–40) days, and with method 3 it was 14·8(6·9) (range 8–38) days *Figure 1* demonstrates this graphically

## Discussion

The presacral space left after excision of the rectum allows blood and exudate to accumulate and favours infection Packing of the space was proposed by Miles[19] with two objectives: to support the pelvic peritoneal floor and contribute to haemostasis. Most authors[1–10] have noted the considerable discomfort to the patient and long healing times (2–3 months) Infection may occur as in five of our patients (15 per cent). Irvin and Goligher[5], however, suggested that packing is indicated in the presence of uncontrollable bleeding and perineal faecal contamination.

Primary closure of the perineal wound allows a primary healing rate of more than 40 per cent in most series[1–10,14,15], including this report where healing rates of 53 per cent were observed with method 2 and 85 per cent with method 3. Primary closure is therefore recommended Some[2–6,8] consider that the pelvic peritoneum should always be closed to prevent bowel loops from filling the presacral space and causing intestinal obstruction, perineal eventrations and infection of the space spreading to the abdominal cavity. Closure of the pelvic peritoneum and the bottom of the perineal wound creates a dead space which is difficult to drain, and haematomas may accumulate which can become secondarily infected[9,14] Leaving the pelvic peritoneum open allows loops to occupy the presacral space and obliterate the dead space. The space can be filled with the omentum[8,15,17] or with the uterus[18]. Continuous saline irrigation during the first 24 h will prevent the formation of coagulum and favour primary healing[14].

Leaving the pelvic peritoneum open[9,14] was not associated with a higher incidence of intestinal obstructions, and infection of the perineum did not evolve into diffuse peritoneal sepsis

The highest incidence of primary healing of the perineum (85 per cent) was achieved by leaving the pelvic peritoneum unsutured, irrigating the presacral space and removing the abdominal drains early. These results may be related to bowel loop occupation of the presacral space, continuous irrigation to prevent formation of haematomas, and the use of abdominal drains and their removal in the first 48 h, allowing early patient mobilization and a dry perineum

Method 3 (abdominal drainage) involved the shortest hospital stay (mean 14·8 days). With method 2 (perineal drainage) the mean hospital stay (23·7 days) was shorter than with the packing method but significantly longer than with method 3, and may relate to the higher rate of infection.

Method 3 is the procedure of choice after excision of the rectum, allowing a greater percentage of primary healing, a lower incidence of perineal infection and a shorter hospital stay.

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# Announcement

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## The Society of Minimally Invasive General Surgeons (SMIGS) Why another society?

The above Society was formed following a meeting of interested general surgeons at the Royal Society of Medicine held on 25 February 1991. Following the explosion of laparoscopic cholecystectomy on to the surgical scene in Europe and the USA, the first symposia on this subject were held in this country in Leeds at the General Infirmary (11–12 June 1990) and at St. Mary's Hospital, London (14–15 June and again on 18–19 June 1990). One of the major reasons for founding the Society was to ensure that minimally invasive general surgery was in fact performed by general surgeons. As laparoscopic and minimally invasive surgery had been performed for some years by gynaecologists and urologists and as there were disturbing reports that these types of surgeons, untrained in hepatobiliary surgery, were carrying out laparoscopic cholecystectomies, we felt there was an urgent need for this new society. The objectives were to advance the art, science and practice of minimally invasive surgery,, to advance research and clinical trials and to disseminate knowledge and hold discussions on the results of such research.

One hundred and thirty-two people gave up a Saturday to attend. At the business meeting before the scientific meeting which had been arranged to follow, there was only one lone voice who spoke against the foundation of this new society and that was on the grounds that there were already too many societies, with too many meetings to attend, subscriptions to pay and journals to read. However, those attending unanimously agreed there was a need for this society and the name was then agreed upon as well, although the acronym was not popularly acclaimed

Lord McColl was elected by a very narrow margin to be the first President, Mr R. D. Rosin unopposed to be Honorary Secretary, Mr M. McMahon unopposed to be Honorary Treasurer and Mr R. McCloy to be Symposia Organiser The meeting agreed that the officers could elect a council of seven to ten members to assist them in the running of the Society.

There followed an excellent scientific meeting which, despite the fact that it over-ran, held everyone to the end and was closed by a most erudite lecture delivered by Dr Professor Hans Troidl on 'The Concept, Evaluation and Philosophy of the Future of Minimally Invasive General Surgery'.

The second meeting of the Society was held at the University of Manchester on 8 June 1991. There was more emphasis on other aspects of minimally invasive general surgery and invited lectures were delivered by Professor Hans Becker of the University of Tubingen, Germany on 'Laparoscopic Oesophageal Surgery'; Dr Joseph Petelin of Kansas City, Missouri, USA on 'Laparoscopic Exploration of the Common Bile Duct' and on 'Controlled Trials of Laparoscopic Cholecystectomy – Are they Necessary or Possible?' by Professor Edmund Neugebauer of the University of Cologne, Germany.

The Society already has over 200 members and is arranging 'hands on' workshops at various hospitals in the UK under its auspices at fixed prices. It has agreed to look into the audit of minimally invasive general surgical operations and it hopes to run a register of all these operations. It has accepted an invitation to have a combined meeting with the Association of Surgeons of Great Britain and Ireland in Jersey in April 1992 and looks forward to a much closer link with that parent Association in the future.

**R. D. Rosin**
Honorary Secretary

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# Surgical workshop

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## Proctoscopic polyp delivery after colonoscopic polypectomy

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Colonoscopic polypectomy is a safe and usually uncomplicated routine endoscopic procedure, first described[1] in 1971. Polyps resected during colonoscopy should be retrieved for pathological examination to finalize diagnosis and plan further management. Unfortunately sometimes retrieval may be incomplete, and one of the situations when a polyp may be lost is while the colonoscope is being withdrawn through the anus[2]. We have developed a simple technique using a standard proctoscope to facilitate retrieval of polyps after snare polypectomy.

### Technique

The colonoscope is threaded through a proctoscope whenever the possibility of a polypectomy is envisaged Colonoscopic snare polypectomy is performed in the usual way[2,3] The colonoscope is then withdrawn with the resected polyp held firmly (e g between the jaws of the grasper). Once the tip of the colonoscope with the polyp is in the lower rectum, this is distended with air and the polyp is held against the suction port, suction being applied to help keep the polyp in place. The proctoscope is then advanced and railroaded over the colonoscope into the anal canal (*Figure 1*). At this point the seal between colonoscope and anal canal is lost, making it impossible to inflate the rectum if this has not been done already With the proctoscope firmly in place, the colonoscope with the polyp at its tip is gently pulled through the proctoscope and out.

### Discussion

Polyps resected during colonoscopy should be retrieved for pathological examination to plan further management It is a pity to steer a polyp down the colon all the way to the anal verge, only to have it damaged or even lost by collision with the anal sphincter. Retrieval has been reported as complete in only 83·5–97·9 per cent of patients in various series[4,5].

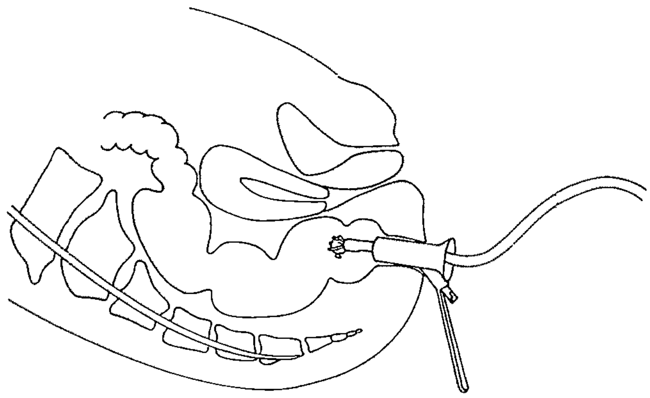

**Figure 1** *Proctoscopic delivery of a polyp after colonoscopic snare polypectomy*

We have developed a simple technique using the standard universally available proctoscope to facilitate retrieval of polyps after snare polypectomy. It has proved to be extremely reliable over 4 years and has lessened the procedure time and patient discomfort Such a simple technique ought to be widely publicized to both surgeons and gastroenterologists alike, since the critical manoeuvre is merely to thread the instrument over the colonoscope before starting the procedure.

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# Temporary loop ileostomy following restorative proctocolectomy

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*A retrospective study compared the outcome of restorative proctocolectomy in patients who had a covering ileostomy* (n = *53*) *with those who had no proximal stoma* (n = *32*). *Those who had a loop ileostomy had a higher incidence of anastomotic leakage* (*21 per cent*), *pelvic abscess* (*32 per cent*) *and postoperative fistula* (*28 per cent*) *than those with no covering ileostomy* (*6, 12 and 12 per cent respectively*). *Intestinal obstruction occurred in 23 per cent of those with an ileostomy, compared with 6 per cent in those who had no stoma. The functional outcome was identical.*

Restorative proctocolectomy with ileoanal anastomosis is an accepted alternative to panproctocolectomy with permanent ileostomy in the management of patients with severe ulcerative colitis[1,2]. Most surgeons advocate the use of a temporary diverting ileostomy to minimize the risk of pelvic sepsis while the anastomosis heals[3]. The temporary ileostomy may be associated with complications such as obstruction and leakage after closure[4], and loop ileostomy increases the duration of hospital stay.

Temporary ileostomy may be omitted under certain favourable circumstances[5,6] and therefore we have retrospectively compared the outcome of restorative proctocolectomy with and without temporary ileostomy.

## Patients and methods

Data were analysed retrospectively from 85 consecutive patients undergoing restorative proctocolectomy between January 1983 and December 1988 Fifty-three patients had a temporary loop ileostomy and 32 had no loop ileostomy. The age and sex distributions were similar in both groups (*Table 1*). The loop ileostomy was closed at a median of 3 months (range 7 weeks to 18 months) from the initial operation. In the majority of cases (45 of 53) closure involved mobilization and simple suture of the ileal defect. More patients in the group without a loop ileostomy had a stapled ileoanal anastomosis (18 of 32, 56 per cent) than in the protected group (11 of 53, 21 per cent).

## Results

The total number of days spent in hospital for restorative proctocolectomy, complications and closure of ileostomy was greater for patients in the ileostomy group (median 28, range 16–160 days) compared with a median of 18 (range 9–64) days ($P < 0{\cdot}001$, Wilcoxon test) The increased time spent in hospital was mainly due to time for closure of the ileostomy (median 6, range 4–40 days).

Postoperative complications are listed in *Table 2*. In the ileostomy group, 12 patients were admitted with small bowel obstruction following closure of their ileostomy, eight of whom settled with conservative treatment Of the four patients requiring surgery, complications in three could be attributed to closure of the ileostomy. Only two patients in the no ileostomy group were admitted with small bowel obstruction, which settled without operation. The incidence of anastomotic leak, pelvic sepsis and fistula was higher in the patients who had a temporary loop ileostomy than in those without ileostomy

Follow-up for patients with an ileostomy (median 53, range 12–92 months) and those having no ileostomy (median 40,

**Table 1** *Comparison of 85 patients undergoing restorative proctocolectomy*

| | Temporary ileostomy (*n* = 53) | No ileostomy (*n* = 32) |
|---|---|---|
| Sex ratio (F M) | 28.25 | 19:13 |
| Median (range) age (years) | 31 (11–62) | 26 (14–63) |
| Stapled anastomosis | 11 (21) | 18 (56) |
| Pouch design | | |
| J | 41 (77) | 26 (81) |
| S | 2 | 0 |
| W | 10 | 6 |

Values in parentheses are percentages

**Table 2** *Complications in 85 patients following restorative proctocolectomy*

| | Temporary ileostomy (*n* = 53) | No ileostomy (*n* = 32) |
|---|---|---|
| Ileoanal anastomotic leakage | 11 (21) | 2 (6) |
| Pelvic abscess | 17 (32) | 4 (12) |
| Fistula | 15 (28) | 4 (12) |
| Pouch cutaneous | 6 | 3 |
| Pouch vaginal | 4 | 1 |
| Ileostomy | 5 | – |
| Ileoanal stricture | 12 (23) | 7 (22) |
| Intestinal obstruction | 12 (23) | 2 (6) |
| Pouchitis | 15 (28) | 7 (22) |
| Failures (pouch excision or ileostomy not closed) | 9 (17) | 2 (6) |

Values in parentheses are percentages

**Table 3** *Functional outcome following restorative proctocolectomy*

| | Temporary ileostomy | No ileostomy* |
|---|---|---|
| No assessed | 44 | 30 |
| Median (range) follow-up (months) | 53 (12–92) | 40 (6–72) |
| Frequency D N (median) | 5 0.0 7 | 4 8 0 4 |
| Urgency | 4 | 3 |
| Soiling D N | 2:8 | 1.6 |
| Incontinence | 4 | 2 |
| Antidiarrhoeals | 20 | 13 |

D N, daytime·night-time, * $P > 0{\cdot}05$ (Wilcoxon $\chi^2$ test)

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range 6–72 months) was not different. The functional outcome in terms of frequency of defaecation, urgency, soiling, incontinence and requirement for regular antidiarrhoeal medication was similar (*Table 3*). Patients whose pouch was excised or who still had a proximal loop ileostomy were excluded from the functional outcome assessment.

## Discussion

Patients with temporary loop ileostomy spend longer in hospital and have a higher morbidity rate than those with no loop ileostomy. In this series, however, patients without a loop ileostomy were a selected group who were considered to be at low risk of developing complications. Although the follow-up period in both groups was similar and omission of a loop ileostomy occurred early in our series there were more 'early' cases in the ileostomy group, and therefore a learning curve effect cannot be excluded.

The potential of a loop ileostomy in reducing pelvic sepsis is not disputed but in selected cases a diverting ileostomy may be omitted without increased morbidity. Criteria for omission of an ileostomy may include: a suitably experienced surgeon, a technically good anastomosis, and whether the patient is fit and not receiving steroids. A prospective controlled study is needed to answer this controversy and to define the criteria for which loop ileostomy is most appropriate.

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# Results of extensive surgery for liver metastases in colorectal carcinoma

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*Hepatic resections were performed during the past 13 years on 31 patients with hepatic metastases from colorectal carcinoma. Of the 31 patients, 22 underwent lymph node dissection of the hepatic hilus. Ten patients underwent removal of recurrent lesions in the liver, lung, adrenal gland and brain after initial hepatic resection. The overall 5-year survival rate was 45 per cent. The outcome for six patients who underwent repeat hepatectomy after an initial hepatectomy was significantly better than for nine patients with unresectable recurrence ($P < 0{\cdot}01$). Six of the 22 patients who underwent lymph node dissection had nodes positive for tumour. Two of the six patients underwent repeat hepatectomy and are alive after 49 and 66 months. Three- and 4-year survival rates of patients with positive lymph nodes were both 40 per cent. Repeat hepatectomy and dissection of hilar lymph nodes improves prognosis in selected patients with hepatic metastases of colorectal cancer.*

The liver is a common site of colorectal cancer metastases. Although patients with hepatic metastases show a high response rate to chemotherapy, 5-year survival is rarely seen[1]. Hepatic resections have been performed for hepatic metastases of colorectal cancer with increasing frequency, and many authors[2–8] have reported 5-year survival rates of 20–54 per cent after such resection. Hepatic resection is a worthwhile treatment for this disease and is no longer considered controversial.

Nevertheless, 79 per cent of patients who underwent hepatic resection had a recurrence within 5 years in one multi-institutional study[9]; 59 per cent of such cases had recurrence in a single organ, and 24·5 per cent in the liver only. Furthermore, 20–30 per cent of patients with hepatic metastases have lymph node metastases in the hepatic pedicle[8,9], and the 3-year survival rate in the literature[8,10] is zero for such patients. Under such circumstances, surgeons must treat these hepatic metastases more aggressively to promote longer patient survival.

We have performed extensive liver resection for such patients during the past 13 years. This article reports the results of hepatic resection, wide lymph node dissection and repeat hepatectomy for patients with hepatic metastases after initial hepatectomy.

## Patients and methods

During a 13-year period from 1978 to 1990, 31 patients underwent hepatectomy for hepatic metastases of colorectal carcinoma at this institution. The median age was 54 (range 27–68) years with a male:female ratio of 16:15. The follow-up period ranged from 2 to 124 months

The locations of the primary lesions were two in the caecum, two in the ascending colon, four in the transverse colon, one in the descending colon, six in the sigmoid colon, and 16 in the rectum. Three patients metachronously had double colon cancers. There were ten Dukes' A lesions, two Dukes' B lesions and 19 Dukes' C lesions. Fourteen patients with metastasis in the liver had a solitary lesion, 11 had two or three nodules, and six had four or more nodules, with the tumour size ranging from 0·3 to 12 cm in diameter When the disease-free interval from resection of primary lesion to diagnosis of hepatic metastases was > 6 months, the metastasis was defined as being metachronous. Thirteen patients had synchronous metastases and 18 patients metachronous. The histological diagnosis of the primary colon cancer was well differentiated adenocarcinoma in 22 patients, moderately differentiated adenocarcinoma in six, poorly differentiated adenocarcinoma in one, and mucinous carcinoma in two.

*Operative procedures*

The operative procedures, terminologically based on Couinaud's nomenclature[11], are shown in *Table 1*. *En bloc* lymph node dissection (clearance of the hepatoduodenal ligament and retropancreatic and coeliac axis nodes) was performed in 22 patients; nine did not undergo node dissection At operation, intraoperative ultrasonography was used to determine the size, location and nature of the tumour as well as its relationship to the vascular system. Such ultrasonography is the most sensitive indicator of the number of lesions present in the liver and demonstrates hepatic venous anatomy well[12]; it was helpful in determining both resectability and the extent of resection required in this series. The tumours were usually removed with a tumour-free margin of > 1 cm.

After discharge from hospital, patients were followed up with the measurement of carcinoembryonic antigen in serum every month and ultrasonographic examination every 3 months at the outpatient clinic. When abnormalities were found on ultrasonography, computed tomography (CT) and hepatic angiography were performed. The criteria for selection for extensive hepatic surgery included: absence of simultaneous metastasis in distant organs, including para-aortic lymph nodes, and no local recurrence; and residual liver function estimated as adequate for the operation to be tolerated.

Ten of the 19 patients who had recurrence after the initial liver resection underwent further resection. A total of 19 operations were performed in these ten patients: eight repeat liver resections in six

**Table 1** *Operative procedures terminologically based on Couinaud's nomenclature*

| Procedure as number of segments resected | No. of patients undergoing hepatectomy | | |
|---|---|---|---|
| | First | Second | Third |
| IV, V, VI, VII, VIII | 2 | | |
| V, VI, VII, VIII and part of IV | 4 | | |
| V, VI, VII, VIII | 8 | | |
| I, II, III, IV | 1 | | |
| IV, V, VIII | 1 | | |
| VI, VII, VIII and part of IV | 1 | | |
| IV, V, VI, VIII | 1 | | |
| VI, VII | 2 | | |
| II, III | 2 | 1 | |
| VII, VIII | 1 | | |
| I, VI | 1 | | |
| VI | 1 | | |
| Partial resection | 6 | 5 | 2 |
| Total | 31 | 6 | 2 |

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patients, eight partial lung resections in five patients and three resections of brain metastases in two. One of eight repeat hepatectomies was combined with right adrenalectomy, including resection of a 5-cm segment of the inferior vena cava followed by reconstruction with expanded polytetrafluoroethylene graft Repeat hepatectomy was performed for patients with single and resectable tumour without simultaneous metastasis to a distant organ. Patients with metastasis of two or three nodules only in a single lung were selected for partial lung resection Operative death was defined as that within 30 days of surgery.

Adjuvant chemotherapy was started from 1 month after hepatectomy in 30 patients. Tegafur (a masked compound of 5-fluorouracil) 800–1200 mg/day was administered orally When patients had side-effects, the dose was reduced or the drug stopped Sixty per cent of patients received the drug for >1 year.

Therapeutic and other factors that may have influenced survival were tested for statistical significance The generalized Wilcoxon test[13] was used to analyse the influence of isolated variables on survival. Overall survival was tested using the Kaplan–Meier method.

## Results

### *Mortality and morbidity*

There were no operative deaths from 31 primary liver resections or from 19 operations for recurrence after the initial liver resection, but there was one in-hospital death (3 per cent). The patient, who underwent liver resection of approximately 84 per cent on CT volume determination, developed postoperative endotoxaemia of unknown origin and deep jaundice, and died from hepatic failure 42 days after surgery. The mean hospital stay for the remaining 30 patients was 28·1 days after liver resection, and 24·6 days for the ten patients who underwent operation for recurrence There was a total of five complications associated with initial extended right hepatectomy including a right lobectomy. There was a total of four complications after 19 operations in the ten patients with recurrence after initial hepatectomy: haemothorax (two), bleeding (one) and right pleural effusion (one). All complications resolved without surgical intervention

### *Outcome after first liver resection*

The median and mean survival periods after first liver resection for all patients in the series were 28·0 and 36·7 months, respectively, excluding the single in-hospital death. Sixteen of the 31 patients are currently alive and 11 have no clinical evidence of recurrent disease. The overall 5-year survival rate was 45 per cent excluding the in-hospital death (*Figure 1*).

The determinants of prognosis were analysed. Sex, age, operation type, number of tumours in the liver, Dukes' classification, location of metastatic lesions and disease-free interval did not correlate with survival. Six patients with a tumour <3 cm in diameter had a 5-year survival rate of 100 per cent, whereas the 3-year survival rate of 23 patients with tumours >3 cm in size was 38 per cent ($P < 0{\cdot}001$) Analysis of the histological grade of cell differentiation of the tumour did not show any significant difference with respect to survival, although the numbers of patients with poorly differentiated carcinoma or mucinous carcinoma were inadequate for evaluation.

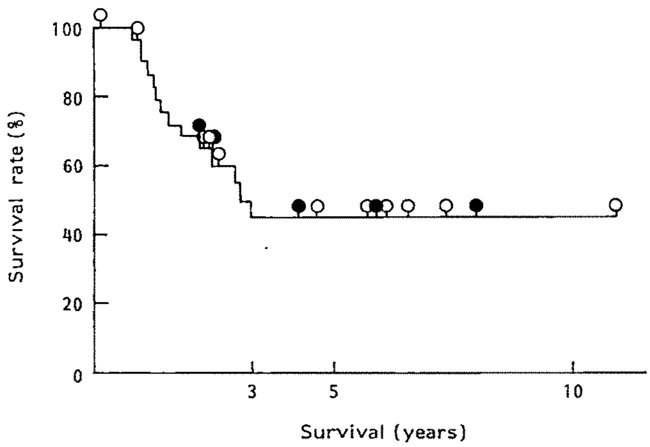

**Figure 1** *Overall survival curve after hepatic resection for patients with hepatic metastases from colorectal carcinoma.* ●, *Alive with recurrence,* ○, *no recurrence*

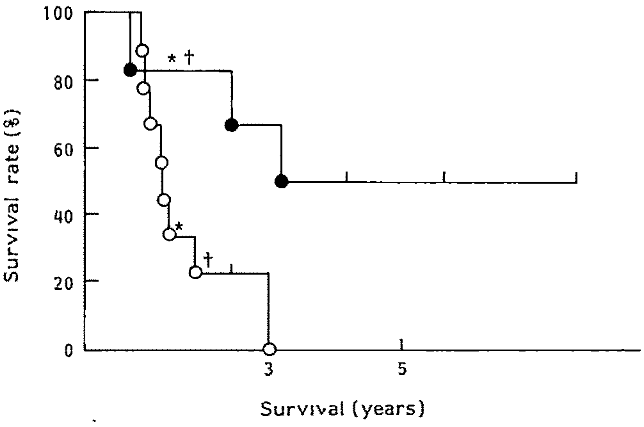

**Figure 2** *Survival curves for patients undergoing repeat hepatectomy* (n = *6,* ⊥, *survived,* ●, *died) and patients with unresectable recurrence after initial hepatectomy* (n = 9; ⊥, *survived,* ○, *died) There was a significant difference between these groups at both *525 days* (P < *0·05*) *and †630 days* (P < *0·01*) *after operation*

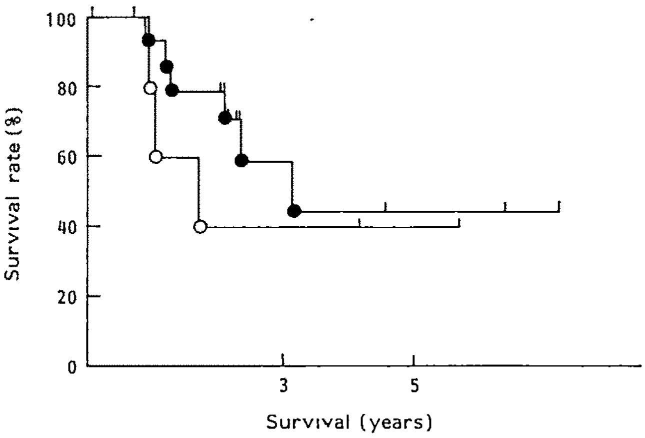

**Figure 3** *Survival curves for patients who underwent hilar lymph node dissection for treatment of hepatic metastases from colorectal carcinoma Curves show patients with positive lymph nodes excluding one in-hospital death* (n = *5,* ⊥, *survived,* ○, *died*) *and patients with negative lymph nodes* (n = *16,* ⊥, *survived,* ●, *died*)

### *Outcome after surgery for recurrent cancer*

Nineteen patients had recurrence after first liver resection and ten underwent treatment by resection. The 2-, 3- and 5-year survival rates of six patients who underwent repeat hepatectomy were 83, 67 and 50 per cent, respectively. All nine patients with unresectable recurrence died within 35 months of the initial hepatectomy Survival in the six patients who underwent repeat hepatectomy was significantly better than that in the nine with unresectable recurrence ($P < 0{\cdot}01$) (*Figure 2*). Moreover, there was a significant difference in prognosis between the ten patients who underwent resection for recurrent disease including resections of brain metastases and the nine patients with unresectable recurrences after the first hepatic resection ($P < 0{\cdot}05$)

### *Significance of hilar lymph node dissection*

Six (27 per cent) of 22 patients who underwent lymph node dissection at the time of the initial liver resection had tumour-positive nodes. These nodes were confirmed histologically at the hepatic hilum in three patients, retropancreatic in two patients, along the common hepatic artery in three, and along the left hepatic artery branching from the left gastric artery in one patient who had metastasis in the left lateral segment. One of the six patients died from postoperative complications.

There was no significant difference in survival between the 16 patients with negative lymph nodes and the five with positive nodes, excluding the one in-hospital death, with 3-year survival rates of 60 and 40 per cent respectively (*Figure 3*). Two of the five patients with positive lymph nodes underwent repeat hepatectomy for recurrent hepatic metastasis, and both are alive with recurrence 49 months and 66 months after the initial hepatectomy. The remaining three patients developed unresectable recurrence in the liver and para-aortic lymph nodes and died 6, 13 and 16 months after liver resection. On the other hand, the 3- and 5-year survival rates of the nine patients who did not undergo lymph node dissection were both 44 per cent.

## Discussion

The median survival of patients with untreated hepatic metastases from colorectal carcinoma has been reported to range from 3·4 to 24 months[14]. Liver metastases are likely to exert a major influence on survival, and liver resection has recently been performed as the best available treatment. In this series, the low mortality (3 per cent) and morbidity (16 per cent) rates after the first liver resection and the zero mortality and 33 per cent morbidity rates in the six patients with recurrence attest to the safety of our approach. These results are comparable to other reports describing a 4–25 per cent operative mortality rate and a 15–50 per cent morbidity rate[2–7,15–17].

There are several controversies concerning the determinants that influence the survival of patients with hepatic metastases of colorectal carcinoma. Although Dukes' classification of primary cancer and the number of metastatic nodules may affect survival[4,16,18], no statistically significant difference was found in the present series, similar to the report of Nordlinger *et al.*[17]. Although Iwatsuki *et al.*[19] advocated extensive operation for hepatic metastases based on their results, in which 96 per cent of 24 patients underwent major hepatic resection, the observation that the type of operation performed was not a prognostic determinant is in general agreement with other studies[2,10] We contend that the efficacy of operation for patients with hilar lymphatic metastases is still open to discussion.

A tumour-free margin of > 1 cm is likely to be an important factor. Although we attempted to achieve a tumour-free margin of >1 cm, no significant difference has been documented[2] in the survival rate between patients having a margin of more than or less than 1 cm. In the present series, only the size of the hepatic metastases showed a statistically significant difference; patients having a tumour <3 cm in diameter had a survival rate of 100 per cent.

Long-term survival reports from the literature are shown in *Table 2*. The majority of the 5-year survival rates reported are in the 16–35 per cent range[2–7]. However, Fortner[10] and Iwatsuki *et al.*[19] obtained favourable results similar to those of the present series.

**Table 2** *Overall survival after hepatic resection for colorectal metastases*

| Reference | No of patients | Survival rate (%) 3-year | Survival rate (%) 5-year | Operative mortality rate (%) |
|---|---|---|---|---|
| Ekberg *et al* [2] | 72 | 30 | 16 | 5·6 |
| Tomas-de la Vega *et al.*[22] | 34 | 33 | 23* | 8·8 |
| Nordlinger *et al.*[17] | 80 | 40·5 | 24 9 | |
| Adson *et al* [4] | 141 | | 25 | 4 |
| Coppa *et al* [7] | 25 | 58 | 25 | 4 |
| Butler *et al.*[16] | 62 | 50 | 26 | 10 |
| Wilson and Adson[25] | 60 | | 28 | |
| Kortz *et al* [15] | 16 | | 34 | 5 |
| August *et al.*[6] | 77 | 53* | 35* | 0 |
| Fortner[10] | 69 | 65 | 49 | |
| Iwatsuki *et al.*[19] | 24 | 73 | 52 1 | 0 |
| Present series | 31 | 44·7 | 44 7 | 3 2 |

*Data obtained from a figure in the text

A few reports have appeared on the resection of recurrent cancer after liver resection for colorectal metastases[20,21]. Fortner[10] suggested that survival in patients in whom recurrent disease was completely resected was significantly better than in those with unresectable disease. Mean survival reported after second hepatectomy has varied from 20 to 31 months[10,20–22]. The present results are comparable to these reports, and the overall survival rate of patients with colorectal metastases was improved.

The presence of lymphatic metastases in the hepatic and coeliac nodes that drain the liver is an important prognostic factor[8 23]. Positive lymph nodes at the hilus may be thought to represent the occurrence of lymphatic remetastasis from established hepatic metastases[24] Fortner[10] observed portal, coeliac or periaortic lymph node metastases in 31 per cent of his patients, and noted that positive lymph nodes were poor prognostic determinants. He emphasized the importance of early detection of liver metastases before remetastasis to the hepatic lymph nodes. However, there is little information available on the significance of hepatic lymph node dissection. Some have reported that all patients with positive lymph nodes died within 3 years after liver resection[8–10]. In the present series, two of the five patients with dissection of positive lymph nodes underwent repeat hepatectomy and both are alive at 49 months and 66 months after initial hepatectomy. One may presume that extensive lymph node dissection of the hepatic hilum and repeat hepatectomy both contributed to achieving a good outcome.

We believe that aggressive resection including lymph node dissection of the hepatic hilum and repeat resection will be helpful in prolonging the life of patients with hepatic metastases from colorectal carcinoma.

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# 'Natural history' of hepatectomy

*The aim of this study was to describe biochemical and liver function test changes after hepatectomy in 33 patients with the following characteristics: absence of underlying liver disease, no blood or plasma transfusion during the perioperative period, uneventful postoperative course. Resection with a temporary pedicle inflow occlusion (10–45 min) consisted of unisegmentectomy or less in 15 patients and bisegmentectomy or more in 18. Blood tests showed: a correlation between aminotransferase rise and duration of ischaemia, and a fall in prothrombin time and factor V levels correlating with the weight of resected specimen at day 1; a moderate γ-glutamyl transpeptidase and alkaline phosphatase elevation and a rise in fibrinogen level correlating with the extent of resection at day 7. Changes in haemoglobin level, white cell count, platelet count, prothrombin time, factor V level and serum bilirubin level tended to return to preoperative levels by day 7. For γ-glutamyl transpeptidase and alkaline phosphatase, increased levels persisted for 8–12 weeks after resection. These results, in this selected group of patients, allow a description of the 'natural history' of hepatectomy. The knowledge of these 'natural' changes may contribute to the early detection of postoperative complications.*

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Despite a dramatic decrease in mortality and morbidity rates following hepatic resection during the last 10 years[1,2], intra-abdominal sepsis, biliary complications and liver insufficiency remain significant problems[3,4]. Diagnosis of these complications requires the collection of clinical, morphological and biological data, including liver function tests. The assessment of tests which aim to evaluate liver function is difficult after hepatic resection. This may be related not only to the extent of the resection and the underlying disease, but also to the volume of blood and plasma transfused[5–7]. The aim of this retrospective study was to observe changes in liver function tests after uncomplicated hepatectomy in a homogeneous group of patients in whom surgery was performed by the same surgeon using a standard operative procedure and in whom no blood or plasma transfusion was given during the perioperative period. In this study, the postoperative changes in liver function tests might reflect the 'natural history' of hepatectomy.

## Patients and methods

The records of 119 patients undergoing hepatic resection between January 1987 and July 1989 were reviewed Data were collected on 33 patients who fulfilled the following criteria. no blood and/or plasma transfusion in the perioperative period, normal residual liver confirmed by surgical biopsy, uneventful postoperative course. There were 27 women and six men with a mean(s.d.) age of 37(13) years, range 21–76 years. Resections were performed for benign liver cell tumours in 23, and malignant tumours in ten (colorectal metastases in nine and fibrolamellar carcinoma in one).

All operations were performed by the same surgeon (J.B ) Laparotomy was by means of a right subcostal incision. Intraoperative ultrasonography was systematically performed to determine the size and location of the tumour as well as the relationship between the tumour and the vascular system. In all cases the resection was carried out with temporary inflow occlusion of the liver. In cases of major liver resection (including more than two segments) the liver was mobilized to expose the inferior vena cava, extraparenchymatous control of both arterial and portal pedicles and the appropriate hepatic vein was achieved before resection Liver transection was performed using Kelly artery forceps and an ultrasonic dissector, haemostasis was secured by sutures and clips. Biological glue was applied to the liver resection margin No biliary drainage was used. Closed abdominal drainage was established by means of a suction drain. In all patients prophylactic antibiotics (cefotaxime 3 g per 24 h) were given for 48 h intravenously Duration of operation and of portal triad clamping were recorded. Resected specimens were weighed.

Blood tests including haemoglobin level, white cell count, platelet count, prothrombin time, factor V level, factor II level, fibrinogen level, and liver function tests (including aminotransferase, γ-glutamyl transpeptidase, alkaline phosphatase and bilirubin level) were carried out before operation and after operation at days 1, 3 and 7. All patients were examined 1 and 3 months after resection; examination included biological tests and liver ultrasonography.

Results are presented as mean values with standard deviation Correlations between all of the parameters with the weight of resected specimen and with the duration of vascular clamping were studied using Spearman's rank test Statistical analysis was performed by $\chi^2$ test.

## Results

### *Operation*

Resection types included local excision (five), unisegmentectomy (ten), bisegmentectomy (nine), trisegmentectomy (one) and quadrisegmentectomy (right hepatectomy) (eight) The mean(s d.) weight of resected specimen was 383(339) g (range 50–1400 g). Patients were classified according to the weight of resected specimen into three groups: group I, < 100 g (*n* = 12); group II, 100–500 g (*n* = 12); and group III, > 500 g (*n* = 9). Group I included all local excisions and seven unisegmentectomies; group II included three unisegmentectomies and all bisegmentectomies; group III included the trisegmentectomy and the eight right hepatectomies. The duration of pedicle inflow occlusion ranged from 10 to 45 min, mean(s.d.) 22(11) min. The mean(s.d.) operating time was 196(54) min, range 60–340 min.

### *Blood test changes after operation*

Results are listed in *Table 1*. The maximal fall in haemoglobin level occurred on day 1 and persisted until day 7. The white cell count doubled from its preoperative level but returned to normal by day 7. A fall in platelet count was observed on day 1 and return to normal was achieved at day 7. Maximal fall in prothrombin time, factor V and factor II levels occurred on day 1; prothrombin time and factor V began to rise again at day 3 and tended to return to preoperative levels by day 7, but factor II remained low up to day 7. The fibrinogen level rose

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**Table 1** *Biochemical changes after hepatectomy in 33 non-transfused patients*

| | Before operation | After operation (days) | | |
|---|---|---|---|---|
| | | 1 | 3 | 7 |
| Haemoglobin (g/dl) | 13·4(1·1) | 12·2(1·5) | 11·7(1·7) | 11·4(1·3) |
| White cell count (cells/mm$^3$) | 6566(1620) | 12 619(3219) | 10535(3036) | 8229(2274) |
| Platelet count ( × 10$^3$/mm$^3$) | 291(64) | 254(62) | 256(72) | 303(109) |
| AST (units/l)* | 20(4) | 280(162) | 108(91) | 63(57) |
| ALT (units/l)* | 20(10) | 420(256) | 270(206) | 161(142) |
| γ-Glutamyl transpeptidase (units/l)* | 61(59) | 47(47) | 63(52) | 117(111) |
| Alkaline phosphatase (units/l)† | 73(35) | 71(31) | 87(36) | 133(93) |
| Bilirubin (μmol/l)‡ | 8·9(4) | 22·2(14) | 23·8(20) | 17·6(21) |
| Prothrombin time (%) | 87(9) | 63(16) | 69(17) | 75(13) |
| Factor V (%) | 94(13) | 63(18) | 78(33) | 79(20) |
| Factor II (%) | 99(11) | 68(15) | 71(30) | 69(20) |
| Fibrinogen (g/l) | 3·7(0·9) | 3·9(1·3) | 4·6(5·5) | 5·8(1·7) |

Values are mean(s.d.). AST, aspartate aminotransferase; ALT, alanine aminotransferase. Normal ranges *10–40 units/l; †25–130 units/l, ‡ < 15 μmol/l

**Table 2** *Haemoglobin, platelet count, bilirubin serum levels and prothrombin time at day 1 according to the weight of resected specimen after hepatectomy in 33 non-transfused patients*

| | Weight of resected specimen (g) | | |
|---|---|---|---|
| | Group I<br>< 100<br>($n$ = 12) | Group II<br>100–500<br>($n$ = 12) | Group III<br>> 500<br>($n$ = 9) |
| Haemoglobin (g/dl)* | 13·1(1·6) | 10·8(1·1) | 12·9(1·3) |
| Platelet count ( × 10$^3$/mm$^3$)† | 285(76) | 257(59) | 212(39) |
| Bilirubin (μmol/l)‡ | 12·75(4·3) | 15·8(7·9) | 36·5(13) |
| Prothrombin time (%)§ | 79·2(7·1) | 64·3(11·1) | 49·4(6·7) |

Values are mean(s.d.). *Not significant; †$r_S = -0·49$; ‡$r_S = 0·62$, §$r_S = -0·79$ (correlations with weight of resected specimen, Spearman's rank test)

progressively after operation up to day 7, but returned to the preoperative level by 1 month. There was a marked rise in aminotransferase levels at day 1, with aspartate aminotransferase (AST) 14 times and alanine aminotransferase (ALT) 21 times the level before operation. At day 7 AST and ALT were respectively three and eight times their preoperative levels. For both γ-glutamyl transpeptidase and alkaline phosphatase, a moderate fall in day 1 level was followed by an increased level at day 7, which persisted for 8–12 weeks after resection. Serum bilirubin level rose up to day 3 but tended to return to normal by day 7.

### *Blood test changes and nature of operation*

Postoperative changes at day 1 are listed in *Table 2* according to weight of resected specimen. The lowest mean haemoglobin level was observed in group II; however, no significant correlation was observed between mean haemoglobin level and weight of the resected specimen. The lowest platelet count was observed in group III, with an inverse correlation between platelet count and weight of resected specimen ($r_S = -0·49$). The highest bilirubin level was observed in group III, with a significant correlation between bilirubin level and weight of resected specimen ($r_S = 0·62$). The lowest prothrombin time was observed in group III, with a significant inverse correlation between prothrombin time and weight of resected specimen ($r_S = -0·79$). A significant correlation was observed between γ-glutamyl transpeptidase at day 3 and weight of resected specimen ($r_S = 0·78$). Fibrinogen level at day 7 was inversely correlated with the weight of resected specimen ($r_S = -0·67$)

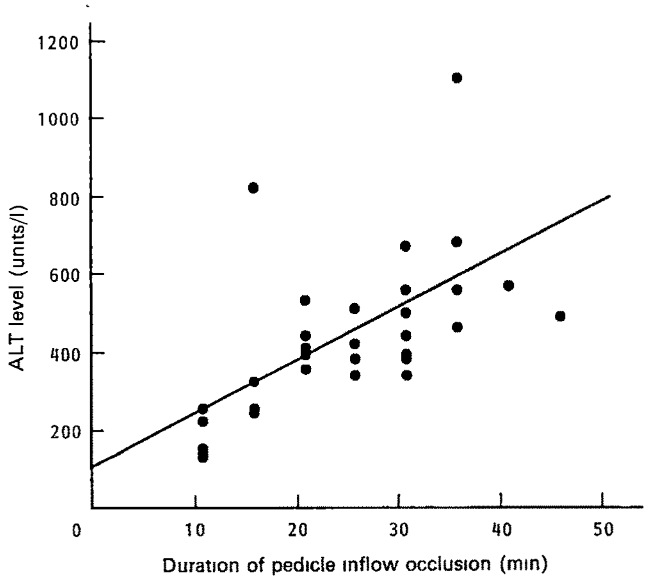

**Figure 1** *Relationship between alanine aminotransferase (ALT) level at day 1 and duration of pedicle inflow occlusion after hepatectomy in 33 non-transfused patients* ($r_S = 0·49$, $P < 0·05$)

No significant correlation was observed between the weight of resected specimen and aminotransferase or alkaline phosphatase levels.

The duration of pedicle inflow occlusion showed a correlation ($r_S = 0·49$) with day 1 levels of both AST and (*Figure 1*) ALT.

## Discussion

During the last decade, despite progress in the surgical technique of liver resection leading to a lower mortality rate, postoperative complications have remained a significant problem[3,4]. The period after operation may be complicated by bleeding, infection and liver failure[5,8,9] A complete assessment using biochemical tests is required for early recognition of these complications. Many studies have tried to evaluate the postoperative biochemical changes in patients after hepatectomy[10–14], but the results of these studies are difficult to analyse because of the inclusion of patients with transfusion, underlying liver disease and in some cases patients with postoperative complications. All these situations are known to modify biochemical tests after surgery[5–7].

In patients with problems such as biliary complications and intra-abdominal sepsis, several biochemical changes can be observed, including prolonged leucocytosis, thrombocytopenia and a rise in aminotransferase and alkaline phosphatase serum levels[3,5,11,15,16]. Persistent decrease in prothrombin time has been observed in postoperative liver failure[4]. In patients with underlying liver disease, the assessment of postoperative biochemical tests is difficult for two reasons. preoperative blood tests are frequently impaired and liver regeneration after hepatectomy can be reduced[17,18]. In transfused patients, many disturbances of biochemical and haematological tests have been described: fall in platelet count, decrease in fibrinogen level and postoperative elevation of aminotransferase and bilirubin levels[1,6,9,11,15].

Minimizing blood loss is a prime concern of the liver surgeon and the avoidance of blood and plasma transfusion is advisable for a number of reasons including transmission of viral disease[19,20], the close correlation between operative blood loss and postoperative complications[15,21,22] and the apparent association between transfusion and increased risk of recurrence of malignant tumours[23]. Vascular clamping is the most effective method of undertaking hepatic resection with minimal blood loss[24,25] The pedicle inflow occlusion induces liver ischaemia and subsequently changes in aminotransferase serum levels[24]. The present results confirm that the rise in transaminases is greatest between days 1 and 2 and that a decrease to normal levels is achieved between days 7 and 10 when no complication occurs[1,5,15]. The amount of liver resected has been implicated in the rise of transaminases after hepatectomy[10,15,22], but no correlation between the extent of resection and aminotransferase levels was found in the present series. On the other hand, a correlation between duration of vascular clamping and aminotransferase level was confirmed[26].

The decrease in haemoglobin level is greatest at day 1, reflecting blood loss. It has been reported that blood loss is significantly higher in major resection than in minor or non-anatomical resection[1,27–29]. Present data do not confirm this relationship. Minimizing operative blood loss is best achieved by avoiding difficult non-anatomical resection where vascular control is less easy.

The only data published regarding posthepatectomy leucocytosis are of an experimental study in which a rise in white cells, prolonged over several weeks, is described[30]. Present results suggest that a white cell count above 10000/mm$^3$ at the end of the first week is abnormal and may be related to developing complications.

The immediate fall in platelet count after hepatectomy has been ascribed to transfusion[6,9,15]. The absence of transfusion and the correlation between fall in platelet count at day 1 and extent of resection observed in our patients suggest that this is also due to liver resection.

After hepatectomy, a decrease in prothrombin time and level of factor V followed by rapid return to normal levels with 7–10 days has been reported[14]. Transfusion and the amount of parenchyma resected have both been implicated[5,9,24]. The absence of transfusion and the significant inverse correlation between prothrombin time and weight of resected specimen in the present data suggest that prothrombin time is a sensitive indicator of postoperative liver function. Both factor V and factor II have been considered as useful indicators of postoperative liver function[26]. We confirm that restoration of factor V is achieved by the end of the first week, but factor II returns to normal later in the postoperative period

After hepatectomy, normal or decreased fibrinogen levels have been described[11,21] Decreased levels were often related to multiple transfusions[11] although in the present series a progressive rise during the first week was observed and fibrinogen level at day 7 was inversely correlated with the extent of resection. In those patients without complications the rise in fibrinogen level may reflect hepatic regeneration.

The rise in both alkaline phosphatase and γ-glutamyl transferase after hepatectomy has been reported in clinical and experimental studies[11,16]. Both were considered as indicators of hepatic regeneration[31]. In the present study, without biliary complications, it was confirmed that persistent elevation of alkaline phosphatase and γ-glutamyl transferase is not pathological until 3 months after operation and may also reflect hepatic regeneration.

In several studies, the increase in bilirubin level after hepatectomy has been attributed to transfusion, underlying liver disease, biliary complications and to the amount of parenchyma resected[7,9,11,17,22] The present study demonstrates that the rise in bilirubin level after hepatectomy correlates significantly with the amount of liver resected. It appears to be a highly sensitive indicator of liver function.

The most important finding of this study is that transient common biochemical changes are observed after uncomplicated hepatectomy. Those biochemical changes are related either to the extent of resection or to the duration of operative liver ischaemia. The absence of underlying liver disease and of perioperative blood and plasma transfusion in this selected group of patients allows a description of the 'natural history' of hepatectomy. The knowledge of these 'natural' changes may contribute to early detection of complications after operation.

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# Therapeutic perihepatic packing in complex liver trauma

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*Packing for control of haemorrhage was used in 22 of 294 patients undergoing surgery for liver trauma over a 6-year period. The major indication for packing was transfusion-induced coagulopathy. Sixteen patients had blunt trauma and six penetrating trauma including five gunshot wounds; 19 patients had major right lobe injuries, three left lobe and five also had hepatic vein injuries. Packing provided definitive control of bleeding in 18 patients but four patients had recurrent bleeding due to hepatic artery injury (three) and hepatic vein injury (one); three required further surgery and bleeding was controlled in the fourth by selective hepatic artery embolization. Six patients died and in two of these recurrent bleeding, despite packs, was a contributing factor. Mean blood loss in the six patients who died was 18 (range 10–30) units, compared with 13·1 (range 8–30) units in survivors. Packs were removed from the 16 survivors at laparotomy at a mean of 3·1 days after insertion; six patients rebled during pack extraction and were successfully repacked. Major morbidity occurred in 12 of the 16 survivors. Seven patients developed intra-abdominal sepsis following packing, one of whom died. Therapeutic liver packing provides life-saving control of hepatic bleeding which is frequently aggravated by coagulopathy. This approach permits resuscitation in an intensive care unit and subsequent planned relaparotomy for retrieval of packs and further intervention as necessary.*

Despite improvements in resuscitation and life support systems, mortality rates of approximately 30 per cent still occur in patients with complex liver injuries following blunt trauma[1,2], due largely to uncontrolled haemorrhage from major parenchymal or juxtahepatic venous injury or transfusion-induced coagulopathy[3]. The management of major hepatic venous injuries requires a specific surgical strategy[4], but perihepatic packing and relaparotomy for retrieval of packs, when used for coagulopathy, has allowed satisfactory control of bleeding in up to 80 per cent of this subset of severely injured patients[5–14].

Liver packing was introduced by Pringle[15] in 1908 and modified by Halsted[16]. Increasing experience with primary repair led to the denouncement of liver packing, because of the high incidence of late sepsis and rebleeding of neglected penetrating wounds[17], but in the 1970s Walt[18] and Calne *et al*[19] recommended the limited reintroduction of packing Packing was advocated as either a 'desperation' technique in certain situations[18] or for temporary control of haemorrhage before transfer to a specialized unit where definitive surgery could be performed[19]. Initial success in four patients[19] and a subsequent report of ten patients endorsed the legitimate use of packing in patients with complex liver injuries[6].

The method has not, however, been universally accepted[20,21] or routinely used[1,22]. This report analyses the efficacy of packing in a subset of patients with severe liver injury in whom bleeding could not be controlled by conventional methods and provides further support for the role of perihepatic packing and planned reoperation in selected patients.

## Patients and methods

### *Patients*

The 22 patients in whom therapeutic perihepatic packing was used for control of hepatic haemorrhage form part of a larger group of 294 patients with liver injuries treated during the 6-year period from January 1983 to December 1988 at Groote Schuur Hospital, one of two major trauma referral centres serving a population of 1 2 million in the greater Cape Town metropolitan area Sixteen patients were men and six were women, with an average age of 26 8 (range 14–48) years The majority of patients (16) had blunt liver injuries resulting from road traffic accidents (12), industrial accidents (two), fall (one) and assault (one) One patient had been stabbed, four had low-velocity gunshot wounds (one with multiple bullet wounds of the liver) and one patient had a close-range shotgun injury.

Liver injuries were classified according to the revised scheme suggested by the Organ Injury Scaling Committee, American Association for the Surgery of Trauma, 1988[23] Grade III injuries include lacerations >3 cm parenchymal depth; grade IV include parenchymal injury involving 25–75 per cent of a hepatic lobe, grade V include parenchymal injury involving >75 per cent of a hepatic lobe or juxtahepatic venous injuries of the retrohepatic vena cava or major hepatic veins.

### *Initial management*

Initial evaluation, resuscitation and management of patients admitted with abdominal trauma were performed according to the protocol of the trauma unit Intravenous lines, nasogastric tube and Foley catheter were inserted. Shocked patients had large-bore, upper limb and central venous catheters placed for infusion of resuscitation fluids when injury to major intra-abdominal veins, vena cava or juxtahepatic veins was suspected

### *Surgical strategy*

Most liver injuries (grades I and II) were managed with simple operative techniques Major bleeding from more severe injuries (grades III–V) was managed temporarily by resuscitative liver packing and pressure to allow optimal resuscitation When haemorrhage from complex liver injuries could not be controlled or when evidence of coagulopathy became apparent, perihepatic packing and planned relaparotomy were used. The term therapeutic packing is used in this paper to describe the latter method of treatment

### *Therapeutic perihepatic packing technique*

Dry laparotomy packs with radio-opaque markers were used to obtain tamponade between the body wall and diaphragmatic surface and the liver injury (*Figure 1*). Packing into the liver wound was avoided. Most of the external mechanical pressure for tamponade was provided by the lower rib cage No drains were placed and the abdomen was closed

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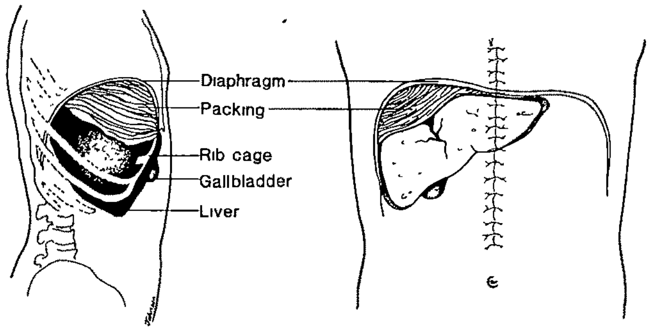

**Figure 1** *Therapeutic perihepatic packing provides tamponade by external counterpressure The edges of the defect should be approximated and packing into the liver wound avoided*

with a continuous non-absorbable suture. Patients were ventilated after operation in an intensive care unit and acidosis, hypothermia, metabolic derangements and dilutional coagulopathy corrected Patients were returned to the operating theatre for pack removal within 72 h The right upper quadrant was irrigated with warm saline to facilitate removal of the final packs. Manipulation was kept to a minimum with debridement of only obviously devitalized liver parenchyma Patients with unexplained postoperative pyrexia underwent ultrasonography or computed tomography (CT), looking for intraperitoneal collections which were initially drained by CT- or ultrasonically-guided percutaneous aspiration or catheter drainage. Laparotomy was used if percutaneous drainage failed or when access for aspiration was unsatisfactory

## Results

### *Presentation and injuries*

Twenty patients were shocked (systolic blood pressure <90 mmHg) on admission and three had no recordable blood pressure on arrival at the unit despite in-transit fluid resuscitation and MAST® antishock trouser suit application (David Clark Company Incorporated, Worcester, Massachusetts, USA). One of these patients underwent emergency thoracotomy and internal cardiac massage in the resuscitation area before laparotomy. All three patients subsequently died.

At laparotomy 19 of the 22 patients had injuries involving the right lobe, these included stellate fractures in eight and extensive lacerations in 11 Three patients had injuries of the left lobe of the liver which involved the medial segment, one patient had extensive lacerations of both medial and lateral segments of the left lobe. Two patients had lacerations involving right and left lobes. Five patients also had major hepatic venous injuries (right hepatic vein· three; left hepatic vein· two patients). One of the 22 had a grade III liver injury, ten had grade IV and 11 grade V injuries

### *Operations*

Major surgery for control of liver bleeding before packing in 15 patients included right hepatic lobectomy (one), segmental or non-anatomical subsegmental resectional debridement of devitalized liver tissue (six), and hepatotomy with intrahepatic ligation of bleeding vessels (eight). In the other seven, ligation of visible vessels was used for bleeding from deep lacerations, and superficial lacerations were controlled by hepatorrhaphy or the use of mattress sutures. Thirteen patients had six packs inserted, seven had fewer and two more. Five patients had hepatic vein injuries, of which four were sutured before packing and one was specifically packed for uncontrolled bleeding from a left hepatic vein injury. Thirteen of the 20 patients in whom postoperative coagulation profiles were performed had laboratory evidence of a coagulopathy.

### *Outcome after packing*

In 18 of the 22 patients packing controlled bleeding, in four bleeding was not controlled and in each of these a major vascular injury was subsequently identified Two patients rebled within 4 h of packing; one had a right hepatic vein laceration requiring a right hepatic lobectomy for control, the other had a right hepatic artery ligation and bleeding was controlled successfully by repacking. Two patients had late rebleeding from the liver 48 h after initial packing; in both cases selective hepatic angiography identified an arterial source of bleeding, which was embolized successfully for definitive control in one patient. The second required laparotomy with ligation of an artery. Both patients subsequently died from multiple organ failure Six patients, including the patient packed for left hepatic vein bleeding, rebled during pack removal and successfully underwent repacking, no further bleeding occurred after pack removal on the second occasion. In two patients minor areas of devitalized liver were excised during pack retrieval.

### *Morbidity*

Major morbidity occurred in 12 of the 16 survivors and included intra-abdominal sepsis (six), bile leaks (five), pneumonia (five), respiratory failure and adult respiratory distress syndrome (three), bronchopleural fistula (one), pleural effusion requiring drainage (one) and renal failure (two) The total duration of primary packing and repacking in survivors was 1–5 (mean 3·1) days. Local intraperitoneal sepsis related to packing developed in seven of the 17 patients who survived more than 3 days, four of six patients packed for 5 days developed sepsis (all four had been packed for a second time) Only three of 12 patients packed for 3 days or less developed infection (including one patient with an incidental amoebic liver abscess which ruptured during trauma).

Analysis of patients with sepsis revealed an associated injury to bowel in two patients and to the bile duct in three. Packing beyond 3 days, or repacking, invariably led to a positive culture from the retrieved packs and subsequent infected collections Endogenous Gram-negative aerobes were the predominant organisms cultured after an associated intestinal or bile duct injury. *Staphylococcus aureus* infection followed packing of more than 3 days or repacking Intra-abdominal sepsis was treated by aspiration (four times) or by laparotomy (seven occasions). One patient had a symptomatic intrahepatic haematoma aspirated percutaneously 28 days after pack removal. The mean duration of hospital stay for survivors was 29·1 (range 9–124) days· for patients with abdominal sepsis 54·8 (range 28–124) days and 13·6 (range 10–24) days in patients without sepsis.

### *Mortality*

Six patients (27 per cent) died within 6 days of operation. Three of these died from head injuries and multiple trauma within 24 h of packing· if these three patients are excluded, mortality was three of the remaining 19 patients (16 per cent). Two of the three patients died from multiple organ failure 48 h after packing and in both recurrent liver bleeding, despite packs, was a contributing factor. One patient died 6 days after initial packing from an *Escherichia coli* septicaemia due to liver and intraperitonal sepsis after colonic perforation and gross faecal soiling sustained during blunt abdominal trauma Mean blood loss in the six patients who died was 18 (range 10–30) units compared with 13·1 (range 8–30) units in survivors

## Discussion

Haemorrhage from liver injuries can usually be controlled by simple methods such as manual compression, hepatorrhaphy or ligation of accessible bleeding vessels within the liver wound[13,22]. In those with major parenchymal or venous injuries, blood loss is often massive, requiring more advanced techniques for control[2,24] Surgical restraint and fewer major resections have resulted in improved survival figures and stressed the role of lesser ancillary procedures for control of bleeding[25,26]· techniques have included hepatotomy or splitting the liver to approach directly deep inaccessible bleeding[2,27], the liberal and longer use of porta hepatis inflow control[28], total hepatic vascular isolation for major venous injuries[4] and liver packing[5–14].

A clear distinction should be made between the two major types of liver packing. Resuscitative packing with manual compression of the bleeding site is an initial measure, used after opening the abdomen, which is effective in controlling or minimizing blood loss while improving haemodynamic stability and repairing other priority vascular injuries, or while awaiting more experienced surgical assistance[23]. A logical extension is to insert packs to achieve haemostasis, close the abdomen and transfer stable patients to trauma referral centres[6,29]. This is one form of therapeutic packing; the other use of therapeutic packing provides tamponade of liver bleeding during definitive surgery when haemorrhage is unmanageable or when coagulopathy develops.

The reported use of therapeutic perihepatic packing varies from 0·5 to 37 per cent, the higher figure skewed by the inclusion of patients transferred to trauma referral centres with packs *in situ*[5–14]. Moore reported a 4 per cent incidence of perihepatic packing in civilian liver injuries treated at eight major North American trauma centres[3]. In a survey of six North American regional trauma referral centres, 25 per cent of patients with major hepatic trauma required packing[14]. In the present study the major indication for therapeutic perihepatic packing was transfusion-induced coagulopathy; thrombocytopenia, qualitative defects of platelet function and coagulopathy, aggravated by shock, hypothermia and acidosis are common after massive, rapid blood transfusion in major liver trauma[30].

Some have expressed doubt on the use of packing for control of active bleeding from intrahepatic or retrohepatic veins[13], but there is evidence from individual cases[31] or small series[19,29,32] where packing temporarily controls this bleeding. In the Louisville study[32] bleeding in four patients with retrohepatic vena cava or hepatic venous injuries was controlled by early packing before development of coagulopathy, three patients underwent definitive repair at a planned second operation after resuscitation and survived. The present report confirms this concept.

Sufficient packs should be inserted to provide adequate external counterpressure. A potential complication from using an excessive number of packs is an increase in intra-abdominal pressure, caval compression and acute renal failure[13]. The critical pressure limit may be avoided by monitoring the intra-abdominal pressure and not exceeding[33] a pressure of 25 mmHg. Others have recommended interposing a plastic adhesive drape[13] folded on itself, microfibrillar bovine collagen (Avitene®; Arnar-Stone Laboratories, McGaw Park, Illinois, USA)[7] or omentum between the dry laparotomy pads and the underlying liver to avoid clot disruption and prevent the pack adhering to the exposed hepatic parenchyma during pack removal.

Rebleeding occurred in four patients with packs *in situ* and was due to a major venous or arterial injury Selective hepatic angiography was helpful in identifying the arterial source of continued bleeding in two instances and gelfoam hepatic artery embolization controlled bleeding in one patient. The use of selective hepatic artery embolization as an adjunct to liver packing in severe liver injury has been reported[34].

Sepsis is the major source of morbidity following packing. Six of the 16 survivors in this series developed sepsis and one patient died of septicaemia, five of these seven patients had an associated bowel or biliary injury, and included the most severely injured patients who had more units of blood transfused and longer periods of hypotension and duration of surgery. Packs were kept in for longer periods in this group, with repacking and a longer total packing duration, which was a major risk factor in the development of sepsis. Removal of packs within 48 h after correction of coagulation and metabolic abnormalities is recommended, and repacking should be avoided if possible. In liver injuries with gross bowel contamination or bile leaks identified during surgery where packing is unavoidable, packs should be retrieved at relaparotomy within 24 h.

## Acknowledgements

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# Hepatic transplantation in children using reduced size allografts

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*The shortage of paediatric liver donors has led to the use of reduced size hepatic allografts. Between July 1987 and July 1990, 30 reduced size orthotopic liver transplantations were performed in 24 children aged between 3 months and 7 years. All patients were in advanced chronic or acute liver failure and were considered unlikely to survive for long enough for a size-matched donor to become available. The most common indication was biliary atresia. The median intraoperative blood loss was 75 (range 13–1015) ml kg$^{-1}$. Nine patients have died and seven have undergone retransplantation, four successfully. Seven patients had portal vein hypoplasia with a high graft failure rate due to ischaemic infarction. There was significant morbidity from biliary tract complications, leading to further operations in four cases. The 1-year actuarial survival rate was 62 per cent.*

The relative shortage of liver allografts that are small enough for paediatric transplantation has led to the development of reduced size liver transplantation (RLT) in Europe[1,2], the USA[3] and Australia[4]. This technique was restricted initially to clinically urgent cases. Increasing numbers of small children, predominantly with biliary atresia, are being referred for transplantation. This report examines 30 RLTs performed between July 1987 and July 1990.

## Patients and methods

The case records of all recipients of RLT were reviewed retrospectively for: indication for transplantation, time on the waiting list, severity of disease (assessed by the Pugh modification of Child's classification), type of graft reduction employed, body-weight, size disparity between donor and recipient, complications and outcome. Data were collected on children receiving whole grafts during the same period as a reference population.

### *Preparation of the allograft*

Allograft reductions were performed as *ex vivo* procedures at the recipient hospital, keeping the organ immersed in ice-cold Ringer's solution.

The hepatic artery and portal vein were dissected and branches to the unwanted lobe or segments were ligated with 3/0 silk. For left lateral segment grafts (segments II and III), the arterial and portal branches to the quadrate (segment IV) and caudate (segment I) lobes were ligated. Only caudate branches were sacrificed for segment II, III and IV grafts.

The biliary system was dissected carefully to avoid skeletonizing the duct, which may damage its blood supply. Lobar grafts were prepared by ligation of the contralateral hepatic duct. Left lateral segment grafts required ligation of the quadrate and caudate lobe ducts. Because these grafts lose a significant arterial supply, from the right hepatic and cystic arteries to the extrahepatic bile ducts[5], the ducts may need shortening. This was done after completing the arterial anastomosis, when the duct was trimmed until there was arterial bleeding from the cut end.

The space between the inferior vena cava and the caudate lobe was developed by sharp dissection for right lobe grafts and segment II and III grafts. The hepatic veins were suture ligated to the unwanted lobes with 5/0 Prolene® (Ethicon Ltd., Edinburgh, UK) before parenchymal section. If the left lateral segment was to be implanted using the Brisbane technique, the inferior vena cava was excised to leave the segmental graft drained by the left hepatic vein[4,6].

The planes of parenchymal section followed the segmental anatomy of the liver (*Figures 1* and *2*). The falciform ligament and ligamentum teres mark the right boundary of the left lateral segment (II and III) (*Figure 3*). Small vessels and biliary radicals were cauterized with bipolar diathermy, and larger vessels were ligated with fine silk ties. Perfusion of the artery, portal vein and bile duct with ice-cold Ringer's solution demonstrated leaks, which were controlled by suture ligation. The cut surface was coated with a fibrin sealant, Tisseel® (Immuno Company, Vienna, Austria).

### *Recipient procedure*

The recipient hepatectomy followed well described techniques[7]. For the Brisbane technique, the inferior vena cava was preserved and the allograft left hepatic vein was anastomosed to an anterior inferior vena cava venotomy[4,8].

Right lobe grafts were inserted in the normal manner. Left lobe grafts were rotated to the right to appose the cut surface and the

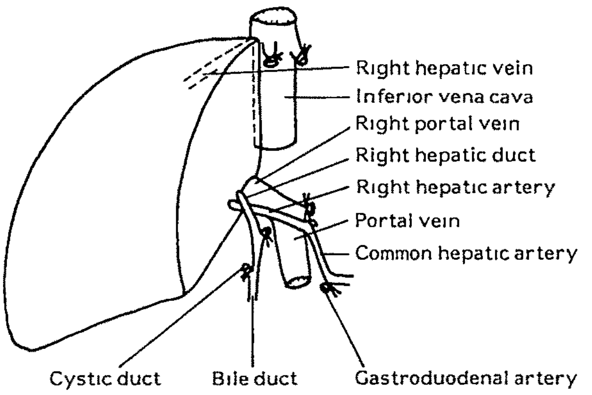

**Figure 1** *Right lobe graft (segments V, VI, VII and VIII)*

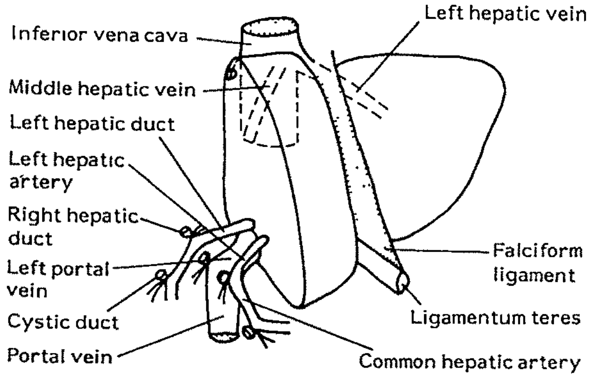

**Figure 2** *Left lobe graft (segments I, II, III and IV)*

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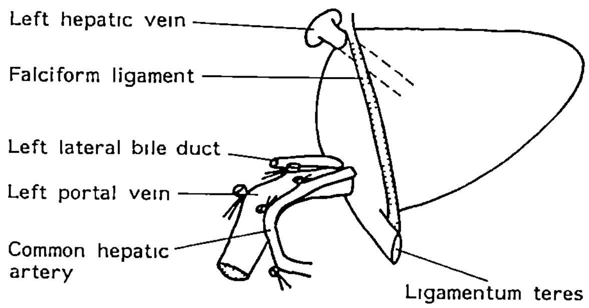

**Figure 3** *Left lateral segment graft (segments II and III)*

diaphragm, to prevent distortion of the inferior vena cava anastomoses by abdominal closure and to reduce the dead space[9]

Portal vein and arterial reconstruction were performed by well described techniques[10–12]. Biliary anastomosis was by end-to-end choledochocholedochostomy or end-to-side choledochojejunostomy, Roux-en-Y, depending on the length of the bile duct and the primary pathology

*Postoperative management*

Patients were returned to the intensive care unit for elective ventilation and monitoring. Prophylactic antibiotics were given at induction, and for 48 h after operation (ampicillin 30 mg $kg^{-1}$ $day^{-1}$ and ceftizoxime 50 mg $kg^{-1}$ $day^{-1}$ in three divided doses). If a Roux loop was constructed then metronidazole, 24 mg $kg^{-1}$ $day^{-1}$ in three divided doses, was added. Antifungal prophylaxis used enteral nystatin, 100 000 units four times daily

Immunosuppression was begun with azathioprine, 2 mg $kg^{-1}$ $day^{-1}$ by infusion, and hydrocortisone, 100 mg twice a day for children under 10 kg and 200 mg twice a day for children over 10 kg Cyclosporin A was given when the patient was haemodynamically stable, at 1 mg $kg^{-1}$ 12-hourly by infusion Oral therapy was used when feeding was re-established, the dose being adjusted according to response and the development of side-effects. Rejection crises were diagnosed histologically and treated with high-dose steroids, or with OKT3® (Ortho-Cilag, High Wycombe, UK) if they were resistant to steroids

*Statistical methods*

Actuarial survival was calculated by the life-table method and comparisons were made using the log rank test

## Results

A total of 53 transplants were carried out in 39 children. 23 whole grafts in 22 and 30 RLTs in 24, six children received both whole and RLT grafts; and one received three RLTs Details of the whole graft and RLT recipients are shown in *Table 1*. The whole graft recipients with chronic diseases were on the waiting list for a median of 50 (range 13–263) days The 15 RLT recipients with chronic diseases had been on the waiting list for a median of 25 (range 5–253) days; all had deteriorated before operation and were inpatients at the time, receiving supplementary enteral nutrition.

The segments used for implantation were: the right lobe once, the left lobe ten times, a trisegmental graft (segments I and IV–VIII) once, and the left lateral segment (II and III) 18 times, using the Brisbane technique on 16 occasions. End-to-side choledochojejunostomy, Roux-en-Y, was performed in 25 cases, and end-to-end choledochocholedochostomy was carried out in five. The anastomoses were usually splinted with either a simple stent or a guttered T tube, although neither was used in three cases. Intraoperative blood loss was related to the use of Tisseel, which was not used for the first six transplants; the median transfusion volume was 120 (range 50–1015) ml $kg^{-1}$ for these operations (equal to 1·9 (range 1·5–15·0) blood volumes) and 70 (range 13–310) ml $kg^{-1}$ for those performed with Tisseel (1·0 (range 0·22–5·29) blood volumes)

*Graft failures*

Thirteen RLT grafts in 11 patients failed, eight due to ischaemic infarction, three due to irreversible rejection, and one each due to massive haemorrhagic necrosis and primary non-function

The child whose first graft suffered primary non-function had a second and successful RLT Two children received a second RLT for irreversible rejection One underwent retransplantation 8 months after his first graft, but again developed severe rejection: increased immunosuppression led to fatal fungal sepsis. The other child developed a bile leak and a faecal fistula after his first graft, both resolved by reducing immunosuppression, but the patient developed irreversible rejection. The faecal fistula recurred after the regraft and he died from bacterial sepsis and chronic rejection. One child suffered irreversible rejection and underwent successful retransplantation with a whole graft.

Three patients whose grafts became ischaemic underwent retransplantation. One had a second successful RLT with portal vein thrombectomy One died after retransplantation with a whole organ, and one was regrafted twice by RLT for hepatic artery thrombosis and is alive and well 11 months after his third transplant The five patients who were not regrafted have died.

Six patients with ischaemic graft failure had significant portal vein abnormalities. Five had hypoplasia and one also had absence of the inferior vena cava. One child had a preduodenal portal vein which was 4·5 mm in diameter, and underwent a portoportal anastomosis utilizing an interposition donor iliac vein graft. The others underwent simple portoportal reconstruction. In each case, allograft perfusion appeared adequate at the time of closure. Two grafts failed due to portal vein thrombosis alone, two were due to portal vein and hepatic artery thromboses, and two were due to ischaemia with patent vessels.

The allograft failure rate for patients with portal vein hypoplasia was 71 per cent All were due to ischaemia and occurred within 3 days of transplantation For children with a portal vein of normal size, the failure rate was 35 per cent.

*Mortality*

Nine patients died, eight have been described above. The other child had a hypoplastic portal vein and no inferior vena cava and died from fungal sepsis 31 days after transplantation; histology of the allograft showed severe ischaemic damage.

The actuarial 12-month survival rate was 62 per cent overall and 77 per cent for patients with a normal-sized portal vein. Six of the nine patients who were under 1 year old at the time of transplantation are still alive The actuarial 12-month survival rate for the whole graft recipients was 77 per cent, not statistically significantly different to the RLT group.

**Table 1** *Details of patients undergoing reduced size or whole graft liver transplantation*

| | Type of graft | |
|---|---|---|
| | Reduced size | Whole |
| No of transplants | 30 | 23 |
| Diagnosis | | |
| Biliary atresia | 14 | 10 |
| $\alpha_1$-Antitrypsin deficiency | 0 | 3 |
| Tyrosinaemia | 0 | 3 |
| Haemangioendothelioma | 0 | 1 |
| Neonatal hepatitis | 1 | 1 |
| Cryptogenic cirrhosis | 0 | 1 |
| Retransplant | 11 | 3 |
| Acute fulminant hepatic failure | 4 | 1 |
| Median age (months) | 14 (3–84) | 25 (7–59) |
| Median weight (kg) | 7·3 (5·8–36) | 9·9(6·8–15) |
| Mean(s.d.) Pugh score | 11·3(1·9) | 9·2(2·5)* |

Values in parentheses are ranges. $^*P < 0.01$, Student's *t* test

### *Biliary complications*

Four patients developed a bile leak: one has been described above, one required reoperation at 13 months, and expectant management was successful in two children. Three patients developed biliary obstruction due to sludging. Two required revision of the biliary anastomosis, at 20 days and at 13 months after transplantation, and one was treated successfully by removal of the biliary stent and use of oral ursodeoxycholate therapy.

### *Other complications*

Three patients had portal vein thrombosis with no other abnormality at the time of transplantation. Simple thrombectomy and portoportal anastomosis was performed in two patients, while one required dissection of the portal vein back to the confluence, to which the allograft portal vein was then anastomosed. Good allograft perfusion was achieved in each case.

Two children had no inferior vena cava and the hepatic veins drained into the right atrium via a common channel. In both, the allograft suprahepatic inferior vena cava was anastomosed to this common channel, and the allograft infrahepatic inferior vena cava oversewn.

One patient had a small native hepatic artery, and the allograft coeliac axis was anastomosed to the infrarenal aorta.

In addition to the reoperations performed for biliary complications, one child was re-explored on the first day after operation for persistent haemorrhage, and another developed an ileal perforation on the 12th day, requiring a local resection. The youngest child developed postoperative abdominal tamponade and required the insertion of a Silastic® (Dow Corning, Reading, UK) prosthesis to expand the abdominal cavity at 24 h.

## Discussion

The overall results are disappointing, with only 15 of 24 patients surviving, four of whom required retransplantation. The most common cause of failure was inadequate allograft perfusion occurring in patients with portal vein hypoplasia. Only two patients with this abnormality survived, one after retransplantation. Portal vein hypoplasia is a recognized risk factor for portal vein thrombosis[10]; in this series it was associated with non-thrombotic hypoperfusion of the allograft. Hepatic perfusion had seemed adequate before abdominal closure. Houssin *et al.*[13] have shown that allograft perfusion falls by 30 per cent with abdominal closure, with a 40 per cent reduction in portal perfusion. This problem might be preventable, or at least detectable, by measuring portal vein flow before closure, a recently adopted practice.

Broelsch *et al.*[5] have reported a 50 per cent incidence of vascular occlusions and graft ischaemia in a series of 14 RLTs. In this series, only one patient with a normal portal vein suffered from this complication, which is not considered to be related specifically to the use of reduced size grafts. The results for patients without portal vein hypoplasia are acceptable, and are comparable to those reported by de Hemptinne *et al.*[9] and Ong *et al.*[14]. With increased experience of the technique, nine of the last ten recipients are alive.

The whole graft recipients are not strictly comparable to the patients with RLT due to the greater number of cases with acute fulminant hepatic or allograft failure in the RLT group, and the higher mean Pugh score in the patients with RLT. The actuarial 12-month survival rate is statistically similar for both groups.

The waiting time for transplantation for all the children in this series was a median of 46 (range 5–263) days. It is difficult to predict accurately how long any patient with chronic liver disease will remain in a stable condition. Deterioration may be gradual or may occur in a stepwise manner due to complications such as infection or variceal haemorrhage. Prolonged delays may allow disease progression to a stage at which the patient is unfit for transplantation.

Major morbidity in this series occurred from biliary tract complications, with four patients requiring intervention. Left-sided grafts are prone to develop proximal biliary ischaemia[5], which caused bile duct necrosis in one child and may have adversely affected biliary reconstruction in others.

In this series the greatest donor:recipient weight disparity which was overcome successfully was 13:2. In one child a ratio of 11:1 prevented abdominal closure, despite using the smallest possible graft. Ong *et al.*[14], using the Brisbane technique, have implanted the left lateral segment from a donor 12 times heavier than the recipient without complication. Body-weight is thus only a rough guide to the size of liver that the recipient can accommodate. All patients with chronic liver disease in this series had ascites, which can stretch the abdominal cavity to almost twice the size expected from body-weight alone[5]: gross splenomegaly may have the opposite effect. Oversized grafts can prevent abdominal closure, embarrass respiration, and become ischaemic[5]. Reduced size grafts can be tailored to the size of the recipient's abdomen. Disparities in vessel sizes may impose an upper limit of donor:recipient size difference: such discrepancies did not pose major technical problems in the absence of portal vein hypoplasia in this series.

The use of RLT can ameliorate the relative shortage of small paediatric organ donors in the UK[7]. The preparation of the segmental graft adds to organ preservation times, but safe preservation for up to 24 h is possible with University of Wisconsin solution[15].

This series of patients represents a high-risk group who received a RLT because it was feared they would otherwise die. These results and those from other centres support the use of RLT in less urgent situations.

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# Case report

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## Hypercalcaemia associated with inflammatory pseudotumour of the spleen

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### Case report

A 57-year-old woman was referred with recurrent intractable hypercalcaemia after initial response to forced diuresis and prednisolone at first diagnosis 3 months earlier. Her serum calcium level had been 4·1 mmol/l (normal 2·2–2·6 mmol/l). Serum parathyroid hormone level was 0·51 mg/ml (normal <0·4 mg/ml) and serum gastrin was 948 pg/ml (normal range 0–100 pg/ml). The possibility of multiple endocrine neoplasm type 1 was considered. Over 2000 Tasmanians belong to one family with this disorder, but no relationship could be traced for this patient.

An abdominal computed tomography scan showed a possible lesion of the pancreas and a 5 cm diameter low-density area with associated calcification in the spleen. Ultrasonography suggested that this was a cystic lesion.

Repeat parathyroid hormone and gastric estimations were within the normal range, but hypercalcaemia required constant infusion with large volumes of fluid.

At neck exploration, four parathyroids 7–10 mm in maximum diameter were identified. Frozen section did not suggest hyperplasia, but in the presence of life-threatening hypercalcaemia (for which no other cause could be found) it was decided to remove three glands completely and half of the fourth.

The patient became hypercalcaemic 10 days after operation, and it was decided to explore the pancreas. The pancreas appeared normal, but palpation of the spleen suggested a solid rather than a cystic lesion, and splenectomy and liver biopsy were performed.

The serum calcium level was 2·3 mmol/l the next day and 1·6 mmol/l 48 h later, before stabilizing at a normal level of 2·20 mmol/l. The patient remains well and normocalcaemic.

#### *Pathology*

The resected spleen was expanded by a solitary circumscribed mass 6 cm in diameter (*Figure 1*) with a peripheral pale yellow zone and a central area of sclerosis. Histological examination revealed a dense lymphoid infiltrate comprising small and large lymphocytes with an admixture of eosinophils and plasma cells in some areas. There was extensive hyaline sclerosis and there were large numbers of non-necrotizing granulomas, which included multinucleated giant cells containing numerous cytoplasmic asteroid bodies (*Figure 2*). Stains for fungi and acid-fast bacteria were negative. No foreign material was identified.

The adjacent splenic parenchyma was normal but scattered small discrete non-necrotizing granulomas were present in adjacent lymph nodes and the liver biopsy.

### Discussion

Inflammatory pseudotumours are mass lesions which can be mistaken for malignancy. They occur in the respiratory tract, gastrointestinal tract, heart, soft tissues and orbit, and have recently been described in the spleen[1,2]. They are characterized histologically by a mixed population of lymphoid cells, histiocytes and fibroblasts, with the frequent presence of non-necrotizing granulomas.

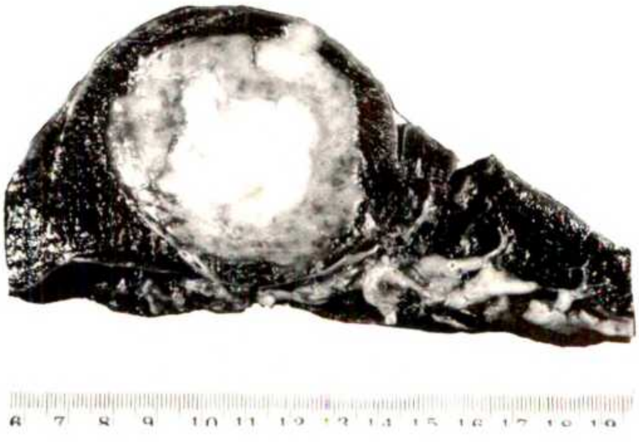

**Figure 1** *Resected spleen*

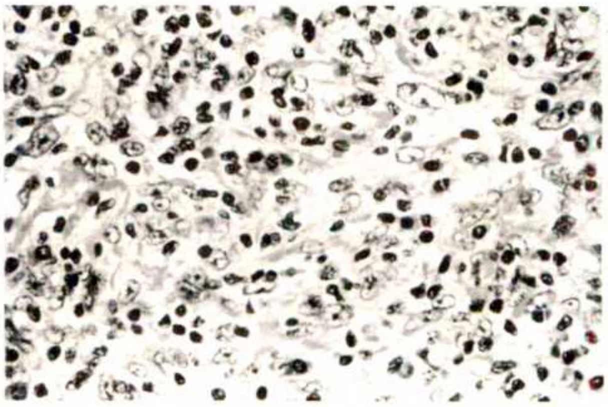

**Figure 2** *Histology of pseudotumour (original magnification × 400)*

In this case, the mixed population of cells made the major differential diagnosis of malignant lymphoma unlikely. Lymphocyte marker studies showed no evidence of a monoclonal population. Differential diagnosis included pseudolymphoma and sarcoidosis. Sclerosis, fibroplastic proliferation and granuloma formation are not seen in pseudolymphoma. Sarcoidosis is not characterized by the presence of a mass lesion, but non-necrotizing granulomas were present in lymph nodes and liver, which is a feature not previously described in association with splenic pseudotumour. The prompt and lasting response to splenectomy suggests that the granulomatous lesions in the liver and lymph nodes played no part in the elevation of calcium levels.

Attempted assay of the preserved specimen for parathyroid hormone related protein was unsatisfactory. Malignant neoplasms that produce this substance are well recognized as a cause of hypercalcaemia. Life-threatening hypercalcaemia may occur in pseudotumours.

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# Simple solution to the short oesophagus encountered at abdominal fundoplication

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Fundoplication is performed by most general surgeons using an abdominal approach, except in patients who are suspected before operation of having a shortened oesophagus. Occasionally after commencing the procedure through the abdomen, the surgeon finds that despite mobilizing the lower oesophagus, insufficient length of intra-abdominal oesophagus is available to perform an adequate fundoplication. The Collis gastroplasty provides a means of effectively lengthening the oesophagus by creating a lesser curve gastric tube[1], but this modification usually requires extension of the wound into the left chest, which adds appreciably to the magnitude of the procedure. We report a simple technique which allows the Collis gastroplasty to be performed without recourse to thoracotomy, using a linear cutter stapling instrument.

## Surgical technique

If after mobilization of at least 10 cm of thoracic oesophagus sufficient intra-abdominal oesophagus is not obtained the decision to proceed to a Collis gastroplasty is made. A 45 Fr oesophageal bougie is passed into the stomach by the anaesthetist as a guide to the diameter of the gastric tube. Thereafter a 1 cm longitudinal, full-thickness gastrotomy is made through both walls of the stomach at the distal limit of the proposed gastric tube. The GIA® 60 (US Surgical Corporation, Norwalk, Connecticut, USA) linear cutter stapling instrument is inserted through the gastrotomy openings (*Figure 1a*). A gastric tube is thus fashioned. The small gastrotomy is repaired and a further continuous suture (Nurolon®; Ethicon Ltd., Edinburgh, UK) is used to invert the staple line (*Figure 1b*). An intra-abdominal Nissen fundoplication fashioned around the lengthened oesophagus completes the operation.

## Discussion

An abdominal approach for the Collis gastroplasty has previously been described using the Auto Suture EEA® circular and GIA staplers[2], but this requires purse-string sutures on both anterior and posterior aspects of the stomach, which may be difficult to insert where access is restricted. The technique that we describe is similar except that instead of creating a hole in the stomach with the EEA instrument, a small incision is made through both walls of the stomach with diathermy. It is a simple task to close this opening with a suture, after the GIA instrument has been fired. The technique described is a quick and safe method of lengthening the oesophagus and fashioning an intra-abdominal fundoplication, using only one stapling instrument and without having to resort to a left thoracotomy.

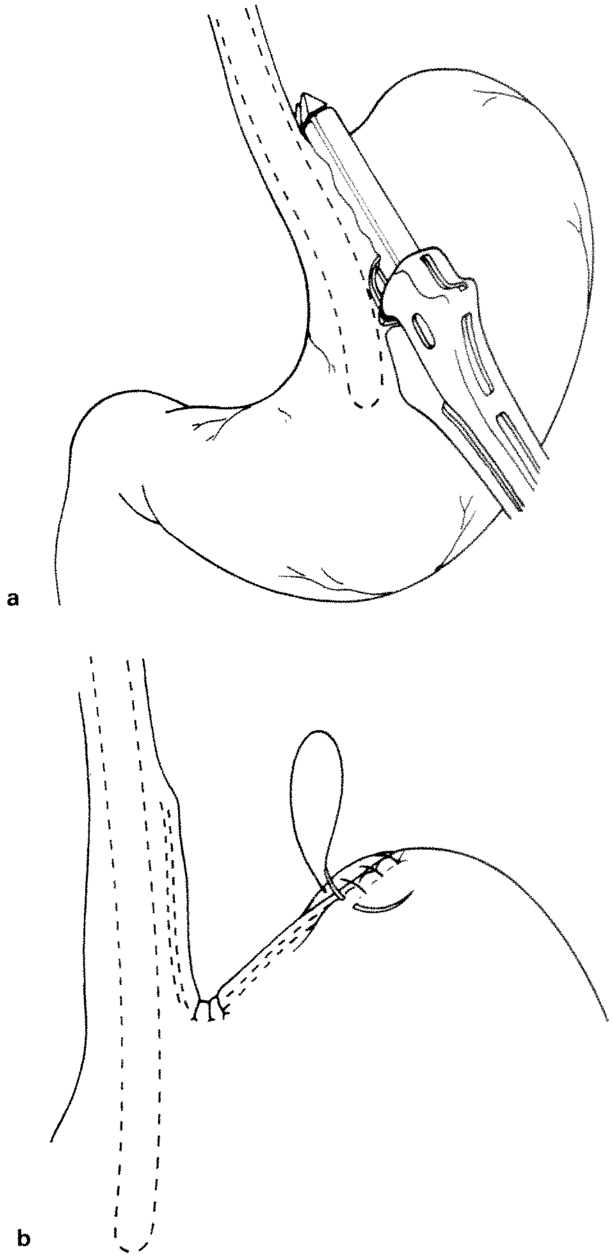

**Figure 1** *Abdominal approach to the Collis gastroplasty:* **a** *a GIA stapler is inserted retrogradely, via a short gastrotomy;* **b** *the staple line is inverted with a running suture*

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52–54

# Effects of fine needle aspiration on subsequent mammograms

*The effects of fine needle aspiration on subsequent mammography were studied in a group of women who were referred with palpable breast lumps. Fifty-two women aged between 36 and 73 (median 53) years underwent mammography before and within 5 days of needle aspiration. Preaspiration and postaspiration mammograms were examined 'blind' by one radiologist. In ten cases, a difference was seen between the preaspiration and postaspiration films. In seven (aged 36–50 years) this was due to aspirated cysts. In three the differences were unexpected and were more significant, although the radiological diagnosis was not altered. If this proportion is extrapolated for a large number of patients then significant numbers of artifacts from fine needle aspiration might be seen on mammograms. It is posssible that some might be interpreted falsely as malignant and some small cancers might be obscured. Women accepted mammography more readily before aspiration than after.*

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Fine needle aspiration biopsy for cytology (FNABC) is being used increasingly to evaluate patients with breast symptoms[1]. When used with mammography and clinical examination it may obviate the need for excision of benign lesions. When immediate reporting is available[2] a diagnosis can be obtained at the first clinic visit. Artifacts on mammograms resulting from FNABC have been described[3] but no studies of the direct effects of FNABC on mammograms have been published.

Recent practice in this clinic was for all symptomatic women to be seen by a clinician before being referred for mammography, where this was indicated. If FNABC was performed it was done at the clinical consultation. Mammography was carried out on the same day or within 4 days. This study looked at the direct effects of aspiration on mammography in a group of 53 patients.

## Patients and methods

Ethical committee approval was obtained for this study. Referral letters were scrutinized for women with palpable lumps. Those who were under the age of 35 years, those who had undergone mammography in the previous 2 years and those with extreme anxiety were excluded. Where the letters indicated palpable lesions for which FNABC would be performed[2], the women were sent directly for two-view mammography before seeing a clinician. If, at the subsequent consultation, aspiration was performed, these women were asked to have a repeat mammogram (aspirated breast only) within the following week. The two mammograms were coded and examined 'blind' by one consultant radiologist (A.J.T.).

## Results

Fifty-two women agreed to this procedure and one refused. The age range was 36–73 (median 53) years. In most cases, the second mammogram was performed 3 or 4 days after the first. Cytology was reported as class I in 30 cases, class II in three, class III in one, class IV in two and class V in five. The seven patients reported as class IV or V had a biopsy which confirmed the lesion to be malignant. The pairs of films for these patients were identical. The aspiration was reported as acellular in 11 women, but in ten of these the palpable lump was cystic.

No difference was seen by the radiologist between the preaspiration and postaspiration films in 42 of the 52 pairs of mammograms. In ten cases, differences were seen but were insufficient to change the radiological diagnosis. Details of these cases are shown in *Table 1*; all had a lesion which proved to be benign. Seven patients had aspiration of cysts; this group comprised younger women (age range 36–50 years) (*Figure 1*).

The other three cases occurred in older women (ages 54, 63 and 68 years) and, although the diagnosis was not altered by the differences in preaspiration and postaspiration films, these patients produced more concern for two reasons: (1) the artifact appeared to be related directly to the aspiration, presumably bleeding, which might mask other lesions in the breast or make interpretation difficult; (2) being older, these women were more likely to have breast cancer.

In two patients, there was more cause for concern as a density was seen in the postaspiration film which was not seen

**Table 1** *Details of the ten pairs of mammograms where a difference was seen*

| Age (years) | Cytology result | Comments on differences between preaspiration and postaspiration films |
|---|---|---|
| 36 | I | Decreased density in outer quadrant of left breast postaspiration |
| 36 | I | Several small cysts in the right breast. Decreased density seen postaspiration in the upper half of the oblique view of the left breast |
| 40 | Acellular | Probable small cyst in lower outer quadrant of left breast. Lesion seen more clearly in preaspiration oblique view |
| 42 | Acellular | Large cystic mass appears a lot smaller on the postaspiration view |
| 43 | Acellular | Cysts seen in both breasts. Preaspiration, round lesion in left breast is larger than postaspiration |
| 46 | I | Probable cysts in both breasts. Slightly decreased density in upper half of postaspiration film |
| 50 | I | Cyst in the upper half of the right breast just above the nipple is less well defined preaspiration |
| 63 | I | Small discrete well defined opacity lying centrally in the medial half of the right breast. Appearances on the preaspiration film suggest an oil cyst, those on the postaspiration film suggest fibroadenoma |
| 54 | Acellular | Localized increase in density in postaspiration film of right breast which is suspected of being blood |
| 68 | I | Postaspiration film has density superior to the nipple which is not present preaspiration |

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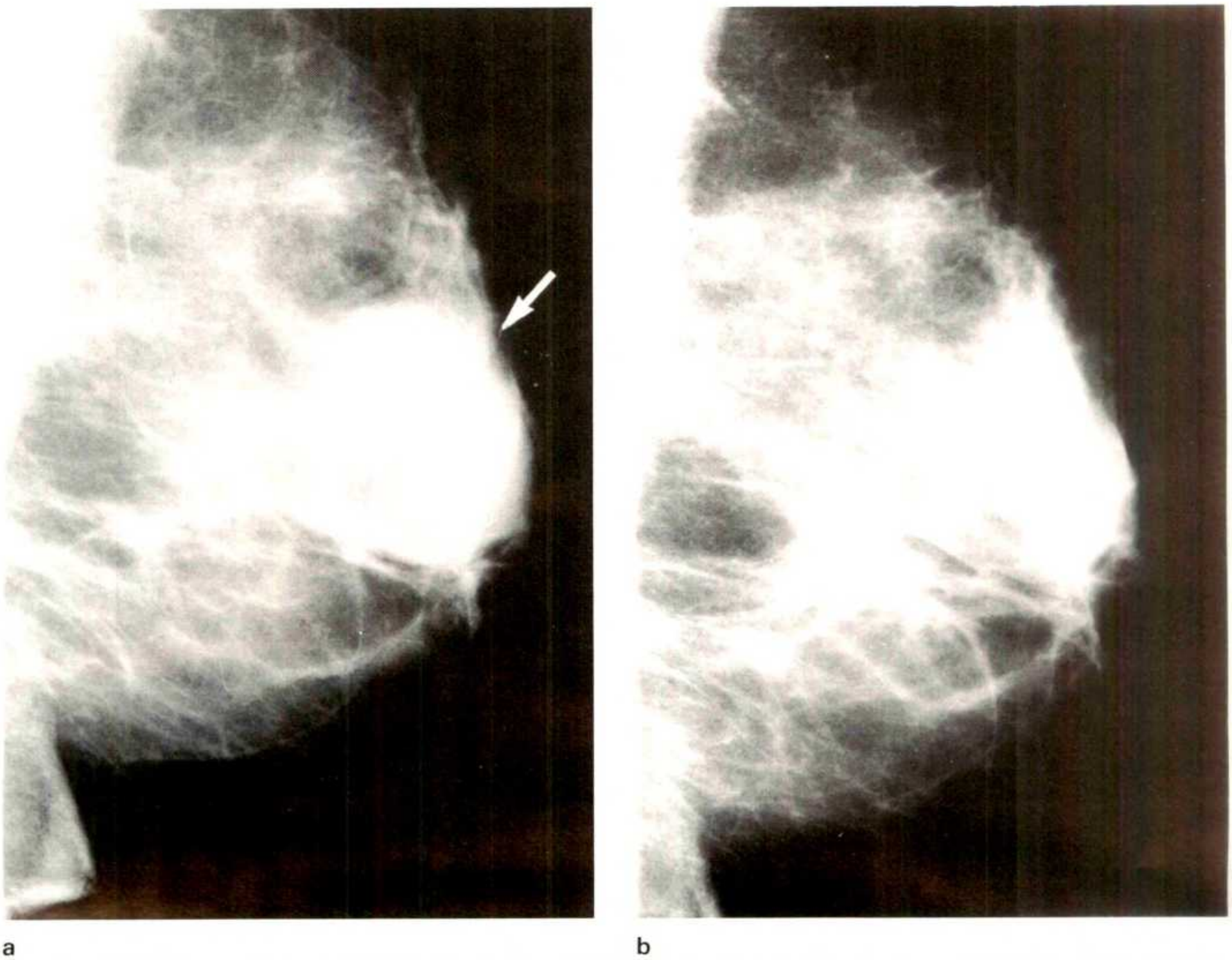

**Figure 1** *Preaspiration* **a** *and postaspiration* **b** *films from a 42-year-old patient presenting with a 27 × 27 mm cystic lump (arrowed) just superior to the nipple in the left breast. On aspiration, this yielded 11 ml of fluid. The postaspiration oblique view shows reduction in this mass compared with the preaspiration view*

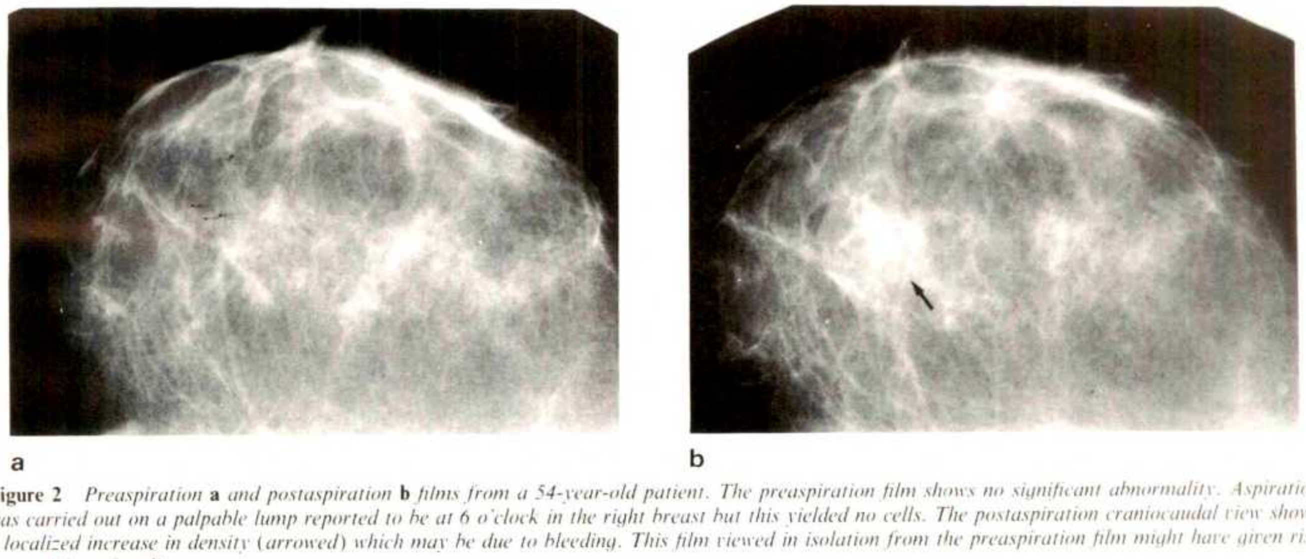

**Figure 2** *Preaspiration* **a** *and postaspiration* **b** *films from a 54-year-old patient. The preaspiration film shows no significant abnormality. Aspiration was carried out on a palpable lump reported to be at 6 o'clock in the right breast but this yielded no cells. The postaspiration craniocaudal view shows a localized increase in density (arrowed) which may be due to bleeding. This film viewed in isolation from the preaspiration film might have given rise to suspicion of malignancy*

before aspiration (*Figures 2* and *3*). The radiologist coded both mammograms as 'probably benign'. Greater concern about the diagnosis would have occurred if the postaspiration films alone had been available.

An unexpected observation has been the difference observed by the radiographers in the attitudes of the women towards undergoing mammography. Under the normal, non-study routine, women arrived for mammography after consultation at the Breast Clinic, where they had answered questions and undergone examination and aspiration. These circumstances make many apprehensive and occasionally quite overwrought, making accurate positioning for mammography more difficult.

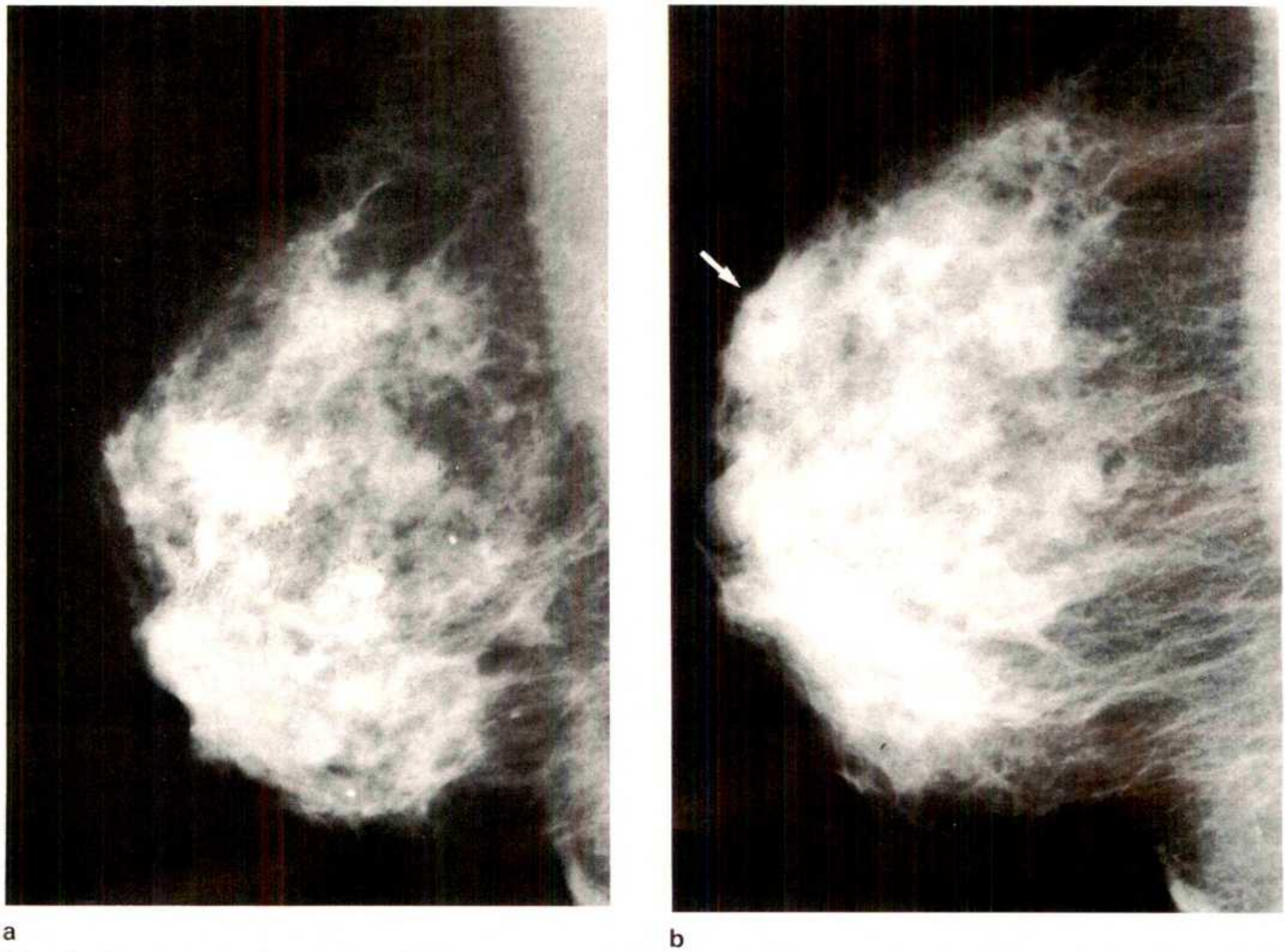

**Figure 3** *Preaspiration* **a** *and postaspiration* **b** *films from a 68-year-old patient. Some duct ectasia and scattered benign type microcalcifications are seen in both breasts but no evidence of malignancy. The postaspiration oblique view contains density (arrowed) superior to the nipple which is not present in the preaspiration view. This corresponds to the site of aspiration. This film, when viewed in isolation, might have given rise to suspicion of malignancy*

Postaspiration pain inhibited proper compression of the affected breast, causing non-uniform exposure of the two breasts. The women in the study, although still apprehensive, were found to be easier to position for mammography because they were less tense and more willing to accept the compression necessary to produce a radiogram of optimum quality.

## Discussion

It is generally accepted that FNABC may cause haematomas. There have been no published studies on the direct effects of aspiration on subsequent mammograms. Sickles and colleagues[3] and Klein and Sickles[4] examined mammograms from 80 women (with 94 breast lesions) who had undergone aspiration in the month preceding mammography. Of the 58 women with indeterminate, rather than cystic or solid, masses an incorrect diagnosis of suspicion of malignancy was given in 17 cases. All these women were found on biopsy or subsequent mammography to have benign lesions. The 17 false-positives occurred when mammography was carried out within 1 week of aspiration and were attributed to the formation of small haematomas. These had the effect of rendering indistinct the smooth edges of benign lesions. Circumstantial evidence for the formation of haematomas is strengthened by the fact that where biopsies were not carried out, the lesions resolved spontaneously.

Appearances were altered unpredictably in only three of 52 mammograms in this study, but if this is extrapolated to the annual throughput of 500 patients there would be approximately 30 artifacts per year. From the characteristics of the three significant alterations observed in this study, it is likely that among 30 such artifacts, some might be interpreted falsely as malignant and some small cancers might be obscured. There were no false-negatives in this study.

The case for performing mammography in patients complaining of lumps before clinical examination and possible aspiration is strengthened by the greater acceptance of mammography before aspiration observed by the radiographers. A new system of clinical practice in this respect has now been introduced and will shortly be evaluated.

## Acknowledgements

We should like to express our thanks to the patients who agreed to participate in this study and to the clinic nurses, radiographers and clinicians for their help. We are also grateful for the support of members of the Ninewells Breast Survey Group.

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# Marking of specimens in patients undergoing stereotactic wide local excision for breast cancer

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With the introduction of breast screening, increasing numbers of impalpable lesions are being identified. After stereotactic or ultrasonically guided fine needle aspiration cytology, lesions can be classified as malignant, suspicious, probably benign or indeterminate[1]. Localized impalpable lesions with malignant or suspicious cytology are currently treated by stereotactic wide local excision. Mammographically suspicious lesions with benign or indeterminate cytology are excised to establish a diagnosis[2]. In those with breast cancer complete excision is important if breast conservation is to be effective[3]. Accurate orientation of wide local excision specimens from patients with palpable breast abnormalities is of value in the assessment of excision margins[4]. It is usual practice to radiograph specimens to determine that the mammographic lesion has been excised[2,5] but orientation of the excision specimen provides valuable information in assessing the completeness of excision of impalpable malignant lesions.

## Technique

When performing stereotactic wide local excision of a breast lesion, tissue anterior to the lesion is excised up to the subcutaneous fat and tissue posterior to the lesion is excised down to the pectoral fascia. The needle localization wire is used as a guide for the other margins of excision. Once the lesion is excised, the specimen is marked by metal Ligaclips® (Ethicon, Edinburgh, UK); one Ligaclip is placed on the anterior margin, two Ligaclips at the medial margin and three at the inferior margin. The specimen is then radiographed, orientating it so that the posterior margin is in direct contact with the radiography plate. Having confirmed that the mammographic lesion has been excised, the completeness of excision can then be assessed. If the lesion approaches any excision margin (*Figure 1*) then further tissue at this margin can be excised and, if appropriate, orientated with Ligaclips before radiography in an effort to obtain a complete excision at one operation. All specimens are then serially sliced and examined by a pathologist. If on histological assessment the tumour approaches any of the excision margins, the pathologist can determine accurately which margin is involved. In patients suitable for re-excision, further tissue can then be removed from the appropriate area.

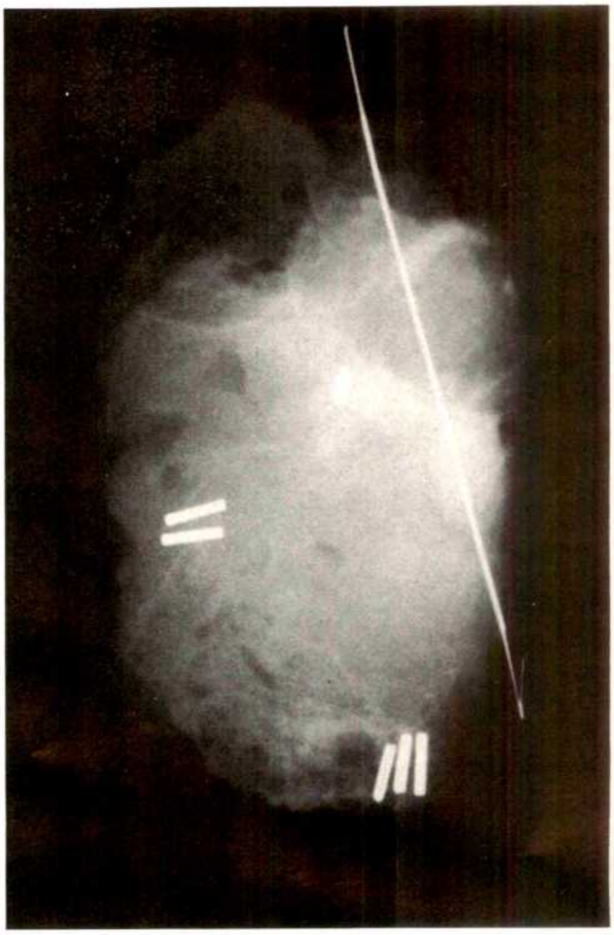

**Figure 1** *Specimen radiograph of wide local excision specimen containing a lesion which yielded malignant cells on stereotactic fine needle aspiration cytology. Note that the lesion appears close to the lateral excision margin. Histology of this specimen showed invasive tumour within 1 mm of the margin of excision. After inspection of the radiograph in theatre, further tissue was removed from the lateral margin. Histology showed all of the margins to be free of tumour involvement and there was no abnormality in the further lateral excision, indicating that excision was complete*

## Acknowledgements

The authors thank Dr A. E. Kirkpatrick, Dr J. Walsh and Dr B. B. Muir for their role in the localization of non-palpable mammographic lesions and Dr T. J. Anderson and Dr D. Paterson for their reporting of needle localization specimens.

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# Outpatient treatment of non-lactational breast abscesses

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*Eighteen consecutive patients with non-lactational breast abscesses have been treated by aspiration (ten patients), surgical drainage after application of local anaesthetic cream (seven patients) or a combination of aspiration and local anaesthetic cream drainage (one patient) combined with a 2-week course of either amoxycillin and clavulanic acid or cephradine and metronidazole. All abscesses resolved completely within 2 weeks of treatment and all 18 patients expressed satisfaction with the method of treatment used. The majority of patients with breast abscesses can now be managed as outpatients.*

Breast abscesses in non-lactating women are now more common than those occurring in the puerperium[1]. Lactational breast abscesses can be treated successfully by recurrent aspiration and antibiotics[2], but it is still traditional to incise and drain non-lactational breast abscesses[1]. In some non-lactational breast abscesses the skin overlying the abscess is thinned and in such patients it was considered that this skin might be adequately anaesthetized by application of local anaesthetic cream. The aim of this study was to determine whether non-lactational breast abscesses can be managed adequately in the outpatient department.

## Patients and methods

Eighteen consecutive patients aged 23–56 (median 32) years with non-lactational breast abscesses have been treated over an 18-month period. Sixteen abscesses were periareolar and the other two were peripheral.

The skin overlying the abscess in ten patients was erythematous and/or oedematous but not thinned. The abscess in these ten patients was aspirated with a 19 Fr (white) needle and syringe and a sample of the pus aspirated was sent for bacteriological examination. The volume of pus aspirated ranged from 2 to 35 ml. Aspiration was repeated at twice-weekly intervals until no further fluid was aspirated. Four patients were aspirated on two occasions, four patients required three aspirations and the other two patients required four aspirations. All patients received amoxycillin and clavulanic acid given as a combined preparation (Augmentin®; Beecham, Brentford, UK) in a dose of 375 mg three times a day orally for 14 days.

In eight patients, the skin overlying the abscess was erythematous and obviously thinned, but not necrotic. Between 3 and 5 g EMLA® cream (each gram contains 25 mg lignocaine base and 25 mg prilocaine base in a eutectic mixture as an oil–water emulsion; Astra Pharmaceuticals, Kings Langley, UK) was applied to the skin overlying the abscess and left in place for a minimum of 1 h. An incision was then made over the abscess, the pus was drained and collected, and the cavity was irrigated with antiseptic solution. Pus from every patient was sent for bacteriological examination. Dry dressings were then placed over the wound and changed at 48-h intervals. All patients reported some minor discomfort during irrigation, but no patient reported any pain during the skin incision. One patient had two components to her abscess: a superficial and a deep component. The superficial component was drained using a local anaesthetic cream and the deep component was aspirated twice a week until no further pus was aspirated. This patient required five aspirations. Samples of pus from both components of the abscess were sent for bacteriological examination. Seven patients, in addition to drainage of the abscess, received the combined amoxycillin–clavulanic acid preparation in a dose of 375 mg three times a day for 14 days and the other patient, who had a penicillin allergy, was treated by a 14-day course of cephradine 500 mg four times a day and metronidazole 200 mg three times a day.

All samples of pus were sent for aerobic and anaerobic culture using bacteriological methods previously described[3].

After resolution of infection, patients were asked whether they would wish to have the same method of treatment if they had a further abscess or whether they would prefer the abscess to be drained under general anaesthesia.

## Results

All abscesses in both groups resolved completely within 2 weeks. Four patients have developed further infective problems after a median follow-up of 9 months. Two patients developed a recurrent abscess. This was again successfully treated by aspiration in one and local incision in the other, and both patients have had elective surgery performed under general anaesthesia to excise the involved duct system. Two patients developed a mammillary fistula after incision of a periareolar abscess and both have been treated successfully by surgical excision under general anaesthesia.

### *Bacteriology*

There were 19 samples of pus sent from the 18 patients, one patient having a superficial and a deep component to her abscess. Single species of organisms were isolated from 15 of the 19 samples. As the same organism was isolated from the two samples of pus sent from the same patient, the bacteriological data presented in *Table 1* relate to numbers of patients. All four patients who developed recurrent breast abscesses or mammillary fistulae had anaerobic bacteria isolated from their breast abscess. Four samples of pus were sterile; these patients had received seven previous courses of antibiotics before being seen at the hospital.

### *Patient satisfaction*

All patients indicated that they were happy with aspiration or local anaesthetic cream drainage and none stated that they would choose to have a subsequent abscess drained under general anaesthesia. Three patients had had a previous abscess drained under general anaesthesia and stated that they much preferred aspiration or local anaesthetic drainage. Five patients reported that they had expected to have their abscess drained

**Table 1** *Bacteriology of pus from 18 patients with non-lactational breast abscesses*

| | Number of patients | |
|---|---|---|
| Organism | Overall ($n = 18$) | Abscess, recurrence or mammillary fistula ($n = 4$) |
| *Staphylococcus aureus* | 4 | 0 |
| Anaerobic *Streptococcus* | 4 | 2 |
| *Bacteroides* sp. | 6 | 2 |
| No growth on culture | 4 | 0 |

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under general anaesthesia and were relieved when this was not necessary.

## Discussion

Reports of successful treatment of non-lactational breast abscesses by aspiration and oral antibiotic treatment have been published[4,5]. In these reports, aspiration was performed once and appropriate antibiotics were not always given. Repeated aspiration is necessary for complete resolution of lactational breast abscesses[1] and also appears to be necessary in non-lactational breast abscesses[6]. A wide spectrum of both aerobic and anaerobic organisms cause non-lactational breast infection[1,3,7], and antibiotics which are effective against this range of bacteria include combinations of amoxycillin and clavulanic acid and of cephradine and metronidazole. It is of interest that the patients who developed recurrent breast abscesses or mammillary fistulae had anaerobic organisms present within their abscesses. All four of these abscesses were situated in the periareolar region, and these patients were shown by subsequent histology to have periductal mastitis, from which anaerobic bacteria can often be isolated[3,7]. It may be that patients with anaerobic organisms and periductal mastitis are more likely to develop recurrent abscesses or mammillary fistulae.

Although ethyl chloride can be used to anaesthetize the skin overlying the abscess, it has been the author's experience that patients experience pain and discomfort during application of this spray; discomfort is not experienced during application of EMLA cream. Incision and drainage of non-lactational breast abscesses using this local anaesthetic cream has not previously been reported. This study shows that where the skin overlying the abscess is thinned, sufficient anaesthesia can be obtained with EMLA cream to allow adequate incision and drainage.

After incision and drainage of a non-lactational breast abscess, up to one-third of patients will develop a mammillary fistula and require an operation to excise the fistula[1]. The method of treating a breast abscess is unlikely to have any effect on the development of such a fistula. Some authors have recommended excision of the abnormal duct at the time of incision and drainage of a breast abscess[8] but this is difficult in the presence of pus and inflammation. Incision and drainage using local anaesthetic cream or aspiration as treatment for non-lactational breast abscesses avoids a general anaesthetic in the majority of patients and allows subsequent elective excision of those mammillary fistulae which do develop, by a surgeon with experience of this condition.

One argument against aspiration of breast abscesses is that these abscesses are frequently loculated. This may be one reason why multiple aspirations are required, although it is of interest that the first aspirate consists of pure pus, whereas the second and subsequent aspirates change from haemo-pus to serous fluid. It is more likely that the majority of breast abscesses are not loculated and the importance of such loculi has been overemphasized.

The question which must now be answered is what constitutes the best practice for treatment of non-lactational breast abscesses. All patients treated by aspiration or local anaesthetic drainage in the present series expressed satisfaction with their treatment. Drainage under general anaesthesia usually requires hospital admission and regular wound dressings for up to 6 weeks. In contrast, local anaesthetic cream drainage or aspiration combined with a course of oral antibiotics produced resolution of all breast abscesses treated in this series within 2 weeks. Although these patients required regular medical attention during this period, the cost of this is still considerably less than a hospital admission and a general anaesthetic If similar results can be obtained in other centres and patients in these centres also indicate a preference for this method of treatment, outpatient treatment of non-lactational breast abscesses should become best practice.

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# Breast abscesses and cigarette smoking

*An 11-year retrospective review of women with breast abscesses presenting to a district general hospital was performed. A total of 122 women were identified with a breast abscess: 85 (70 per cent) with non-lactational abscesses and 37 (30 per cent) with an abscess in the puerperium. Six of 37 lactational and 24 of 85 non-lactational abscesses recurred. Sixteen mammillary fistulae developed, all following incision and drainage of non-lactational breast abscesses. Women with non-lactational breast abscesses were more likely to smoke cigarettes* ($P < 0{\cdot}005$)*. Breast abscesses containing anaerobic bacteria were significantly more likely to occur in current cigarette smokers* ($P < 0{\cdot}05$)*. Women with non-lactational breast abscesses who were heavy cigarette smokers were more likely to suffer recurrent abscesses* ($P < 0{\cdot}01$)*. There was histological evidence of duct ectasia on biopsy in 25 women with non-lactational abscesses and 21 of 25 were current smokers. Mammillary fistulae developed more frequently in current smokers* ($P < 0{\cdot}03$)*. Cigarette smoking is important in the natural history of non-lactational breast abscesses and may predispose to anaerobic breast infections and the development of mammillary fistulae.*

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The incidence of lactational breast abscesses is declining but non-lactational breast abscesses are seen more frequently[1,2]. Non-lactational breast abscesses often recur and may be associated with mammillary fistulae or mammary duct ectasia[1,3,4].

This study examined the factors which might predispose women with non-lactational breast abscesses to develop further sepsis.

## Patients and methods

The case records of all women presenting with a diagnosis of a breast abscess over an 11-year period were reviewed (1 January 1980–31 December 1990) Breast abscess was defined as an acute inflammatory lump which yielded pus on incision Details were recorded of the clinical features, smoking habits, surgical treatment and eventual outcome in all women.

From 1980 the Nursing Kardex and Selly Oak Hospital Medical Admissions Chart required the patient's smoking habits to be recorded A patient was recorded as smoking currently and the number of cigarettes smoked per day noted Light smokers were defined as women smoking 1–10 cigarettes/day and heavy smokers as women smoking 11 or more cigarettes per day Women were recorded as 'never smoked' if at admission they did not smoke unless the case notes recorded that they had previously done so When a breast biopsy had been taken histological details were recorded Bacteriological details were noted for all patients Histological specimens were reviewed to confirm the presence of dilated ducts and for acute/chronic inflammation surrounding the ducts[5].

## Results

A total of 122 women presented with a breast abscess over the 11-year period. Several patients had experienced more than one episode of abscess formation but for the purpose of the study only the first presentation was considered

### *Lactational breast abscesses*

Thirty-seven (30 per cent) women (mean age 25·4 (range 16–41) years) had lactational abscesses incised and drained. Eight women were breast feeding at the time of presentation and the remainder were pregnant ($n = 4$) or in the puerperium ($n = 25$)

Nineteen women were non-smokers, eight women previously smoked and ten were currently cigarette smokers. *Staphylococcus aureus* was isolated from 27 patients, anaerobic bacteria from four, coliform bacteria from one woman and no growth was obtained from five women.

Six women developed recurrence of their abscess, four who had never smoked, one who was a previous smoker and one who was currently smoking 20 cigarettes per day. Biopsy of the cavity wall from ten women (including all six with recurrent abscesses) failed to show any evidence of mammary duct ectasia

### *Non-lactational breast abscesses*

Eighty-five women (70 per cent) (mean age 35·8 (range 11–69) years) had non-lactational breast abscesses incised and drained. Twenty-eight (33 per cent) had never smoked, eight had previously smoked and 49 (58 per cent) were currently doing so regularly (*Table 1*). Smoking habits were not age-related (*Table 2*)

Women with non-lactational breast abscesses were more likely to be current smokers ($\chi^2 = 9{\cdot}6$, $P < 0{\cdot}005$) and more likely to have ever smoked (relative risk 2·15, 95 per cent confidence interval 2·04–2·26) than women with lactational breast abscesses.

The bacteria isolated from the initial abscess are listed in *Table 3*. Fifteen of 18 women who developed anaerobic breast

**Table 1** *Smoking habits of women with non-lactational breast abscesses*

| | $n$ | Recurrent abscess | Mammillary fistulae |
|---|---|---|---|
| Never smoked | 28 | 3 | 2 |
| Previous smokers | 8 | 1 | 1 |
| Current smokers | | | |
| Light (≤10/day) | 13 | 4 | 3 |
| Heavy (>10/day) | 36 | 16 | 10 |
| Total | 85 | 24 | 16 |

Heavy smokers are more likely to develop a recurrent non-lactational abscess, Armitage test for trend, $\chi^2 = 7{\cdot}10$, $P < 0{\cdot}01$ Mammillary fistulae are more likely to occur in current smokers, Fisher's exact test $P < 0{\cdot}03$

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**Table 2** *Frequency of smoking in women with non-lactational breast abscesses*

| Age (years) | Total | Current smokers | Previous smokers | Never smoked |
|---|---|---|---|---|
| 15–24 | 19 | 10 | 1 | 8 |
| 25–34 | 19 | 13 | 2 | 4 |
| 35–44 | 25 | 16 | 3 | 6 |
| 45–54 | 13 | 7 | 2 | 4 |
| 55–64 | 3 | 2 | 0 | 1 |
| ≥65 | 6 | 1 | 0 | 5 |
| Total | 85 | 49 | 8 | 28 |

**Table 3** *The relationship between bacterial isolates and duct ectasia in non-lactational abscesses*

| | $n$ | Recurrent abscess | Abscess biopsied ($n = 32$), duct ectasia confirmed histologically |
|---|---|---|---|
| *Staphylococcus aureus* | 31 | 6 | 2 |
| Anaerobic bacteria | 18 | 9* | 9† |
| No growth | 32 | 7 | 13† |
| Coliform bacteria | 4 | 2 | 1 |
| Total | 85 | 24 | 25 |

*The presence of anaerobic bacteria in the initial abscess is associated with recurrence, $\chi^2 = 4{\cdot}1$, $P < 0{\cdot}05$; †a biopsy showing duct ectasia was associated with a current or previous abscess containing bacteria other than *Staphylococcus aureus*, $\chi^2 = 9{\cdot}8$, $P < 0{\cdot}005$

abscesses were current cigarette smokers compared with 34 of the 67 women who had other organisms isolated or showed no bacterial growth ($\chi^2$ test with Yates' correction = 4·9, $P < 0{\cdot}05$).

Twenty-four women developed further breast abscesses following incision and drainage and 16 went on to develop mammillary fistulae. Heavy smokers were significantly more likely to develop further breast abscesses (Armitage test for trend, $\chi^2 = 7{\cdot}10$, $P < 0{\cdot}01$). Women with anaerobic breast abscesses were more likely to develop recurrent breast abscesses ($\chi^2$ test with Yates' correction = 4·1, $P < 0{\cdot}05$; *Table 3*). Mammillary fistulae developed from non-lactational breast abscesses significantly more often in current smokers ($P < 0{\cdot}03$, *Table 1*)

Thirty-two women underwent biopsy either at presentation or on recurrence of their abscess and review of the histology revealed 25 women had mammary duct ectasia. The majority of the biopsies were taken when the patients returned with a recurrent abscess or fistula but three women had a biopsy at first presentation which was diagnostic of duct ectasia. Among the 25 women with a histological diagnosis of duct ectasia, 21 were current cigarette smokers, one woman had previously smoked and three had never done so. A bacterial isolate other than *Staphylococcus aureus* from the initial abscess was significantly more likely to be associated with a later histological confirmation of duct ectasia ($\chi^2 = 9{\cdot}8$, $P < 0{\cdot}005$; *Table 3*).

## Discussion

Despite the reported fall in the incidence of lactational breast abscess elsewhere[1,2] they accounted for one-third of the abscesses in this series. They were usually associated with *Staphylococcus aureus* and did not tend to recur. When lactational abscesses did recur this could not be related to smoking habit.

Non-lactational breast abscesses tend to recur and three factors have been associated with recurrence; subareolar site[1,3], anaerobic bacteria in the abscess[1,3] and the presence of underlying duct ectasia[1,3].

There was no difference between peripheral and subareolar abscesses and although breast abscesses containing anaerobic bacteria were more likely to recur, it was not the most significant factor. The association of histological duct ectasia with recurrence may be because recurrent abscesses tend to be subject to repeated biopsy and this leads to the possibility of an ascertainment bias. It is likely that duct ectasia is responsible for the majority of these abscesses even when histological confirmation is not obtained[5,6].

The aetiology of subareolar sepsis remains unknown. Cigarette smoking is reported to reduce the incidence of benign breast biopsies[7,8] by lowering plasma and urinary oestrogen levels[7]. The Office of Population Censuses and Surveys reported that in 1988, 17–39 per cent of women were current smokers, the variance being related to social class and age[9]. A recent survey in the Selly Oak Hospital District has shown that approximately 30 per cent of the female population currently smoke and 10 per cent have previously done so[10]. Regardless of age 67 per cent of women with non-lactational breast abscesses and 84 per cent of women with a histological diagnosis of duct ectasia currently smoke or have previously done so. Smoking may be an aetiological agent in this condition. This is supported by the higher recurrence rate of non-lactational breast abscesses in women who are heavy smokers and the association of smoking with anaerobic breast abscess. The recent increase in cigarette smoking over the last decade in young women aged 20–40 years may account for the apparent increase in the incidence of non-lactational breast abscesses in this period[1,2,9]. The mechanism is not clear but smoking leads to the production of toxins in ductal secretions and this may damage the lactiferous ducts[11,12].

The aetiology of mammillary fistula is unknown[13]. Nipple inversion and squamous metaplasia of the nipple may be contributory but it is likely that such fistulae are complications of duct ectasia[14]. Only seven of the 16 women who developed mammillary fistulae in this series had nipple inversion, in keeping with previous reports[4,14]. Women who were current smokers were significantly more likely to develop mammillary fistulae The high frequency of sterile cultures from the non-lactational breast abscesses and the retrospective nature of this report require prospective studies of this phenomenon.

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# Progress in the management of head injury

*Three 1-year surveys of head injury management spanning a 9-year period in a single regional centre are presented. There was a reduction in total numbers of head injury admissions after guidelines for admission and referral were implemented. More liberal use of computed tomography resulted in detection of a greater number of intracranial haematomas with the majority detected in non-comatose patients. The early mortality rate in severe head injury fell from 45 per cent to 34 per cent despite referral of large numbers of patients with multiple injuries and a substantial proportion (12 per cent) of patients aged more than 70 years in whom outcome did not improve. Total occupied bednights and bednights occupied per surviving patient with severe head injury fell over the period of study. Care for patients with significant head injury should be based on regional neurosurgical units associated with trauma services.*

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Throughout the UK, most patients with head injury requiring hospitalization are admitted primarily to general, orthopaedic or paediatric surgical units. A small proportion (3–5 per cent) are referred to a regional neurosurgical unit[1] because of deterioration in the level of consciousness, abnormal neurological signs or seizure activity, that suggest intracranial haemorrhage. Recently, referral to neurosurgical centres has been encouraged for patients who have not deteriorated, but who exhibit certain risk factors, raising the probability that an intracranial haematoma is present; skull fracture in combination with depression of the level of consciousness, or focal neurological signs[2,3]. This pre-emptive approach is preferred because delayed or undiagnosed intracranial haematoma remains a major cause of morbidity and mortality after trauma[4–10]. Other essential factors for prevention of secondary brain damage include adequate resuscitation, control of raised intracranial pressure and avoidance of craniospinal infection.

Consideration should be given to the concept of head injury centres, based on regional neurosurgical units with clinical teams well versed in resuscitation and safe transport, facilities for computed tomography (CT) and neurointensive care to include monitoring of intracranial pressure.

Throughout the study an 18-bed head and spinal injury unit, located in the principal area accident hospital, formed part of the regional clinical neurosciences service; 95 per cent of all head injuries requiring hospital admission and occurring in Edinburgh (referral population 0·6 million) were admitted directly to this unit. All severe and complicated head injuries occurring in south-east Scotland were accepted and the unit cared for 35 per cent of all head injuries requiring hospital admission in the area (referral population 1·2 million).

A survey of patients admitted to this unit in 1981 was reported[11] and surveys in the years 1986 and 1989 have now been carried out. During this period a number of developments relevant to the management of head injury have taken place. In 1982, guidelines regulating admission of cases of minor head injury from the accident and emergency department were introduced. Emphasis was laid upon the identification and admission of patients with depression of the level of consciousness, neurological dysfunction and/or skull fracture[3]. Based on data linking skull fracture with intracranial haematoma, from 1986 early CT was advised for all cases of severe head injury and patients with moderate and minor injury plus skull fracture[12,13]. A more intensive approach was adopted to the management of compromised cerebral perfusion pressure after severe head injury.

The advantage of regionalization of head injury care in association with the regional neurosurgical service was examined. Is expenditure on a head injury unit justified by improvements in head injury management and outcome?

## Patients and methods

During each of the study years (1981, 1986 and 1989), details of each patient admitted to the Edinburgh head and spinal injury unit were obtained prospectively using a standard proforma sheet, and entered into a microcomputer database (dBase® IV, Ashton–Tate, San Jose, California, USA). Data included age, cause of injury, presence of skull fracture and other injuries, neurological status after resuscitation including level of consciousness on the Glasgow Coma Scale, findings of CT, operative treatment and subsequent use of artificial ventilation and intracranial pressure monitoring. Early outcome from injury was scored at discharge from the unit using the Glasgow Outcome Scale.

Patients were divided into three groups according to Glasgow Coma Sumscore (GCS) after resuscitation. Patients with severe head injuries remained in coma, scoring 8 or less with no eye opening, even to painful stimuli. Moderate head injuries included patients who scored 9 to 12 on the GCS and those who scored 7 or 8 but opened their eyes to pain. Minor head injuries scored 13 to 15 points on the GCS. This form of triage fails to take account of localized skull and brain injuries in patients who have not lost consciousness. There is, however, an approximately tenfold difference in mortality between these three grades of head injury[11]. The admission rates, pattern of referral and the prevalence of multiple injuries were examined. These were defined as injuries requiring the services of another surgical specialty. The use and efficacy of CT in detecting intracranial haematoma was assessed. Utilization of beds was evaluated as total occupied bednights and as bednights occupied per surviving patient. Distribution of discrete variables was compared by the $\chi^2$ test using Yates' correction throughout.

## Results

### *Number of admissions and severity of injury*

In 1981 a total of 1919 head-injured patients were admitted to the unit (*Figure 1*). From 1986, the annual number of head injury admissions averaged about 1000 and represented a 46 per cent reduction during the period following introduction of guidelines for admission and seat belt legislation[14].

The distribution of head injuries by severity is shown in *Figure 1*. Severe head injuries have remained fairly constant. The greatest reduction has been in the admission rates of patients with minor head injury (1616 to 702). The numbers of patients graded as having moderate head injury varied.

Total occupied bednights are shown in *Figure 2*. The number

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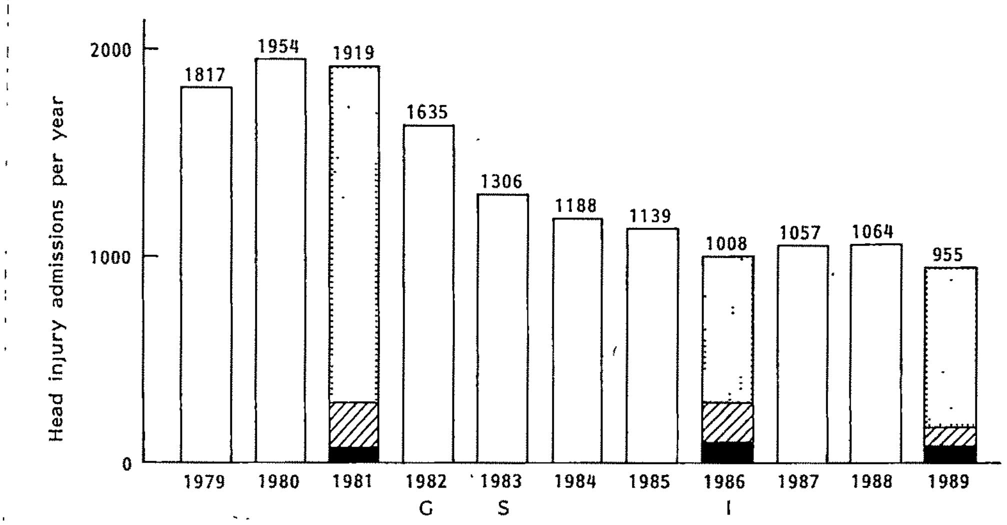

**Figure 1** *Head injury admissions over 1 decade.* ■, *Severe;* ▨, *moderate;* □, *minor,* □, *total. G, guidelines for admission; S, seat belt legislation, I, intensive care unit opened*

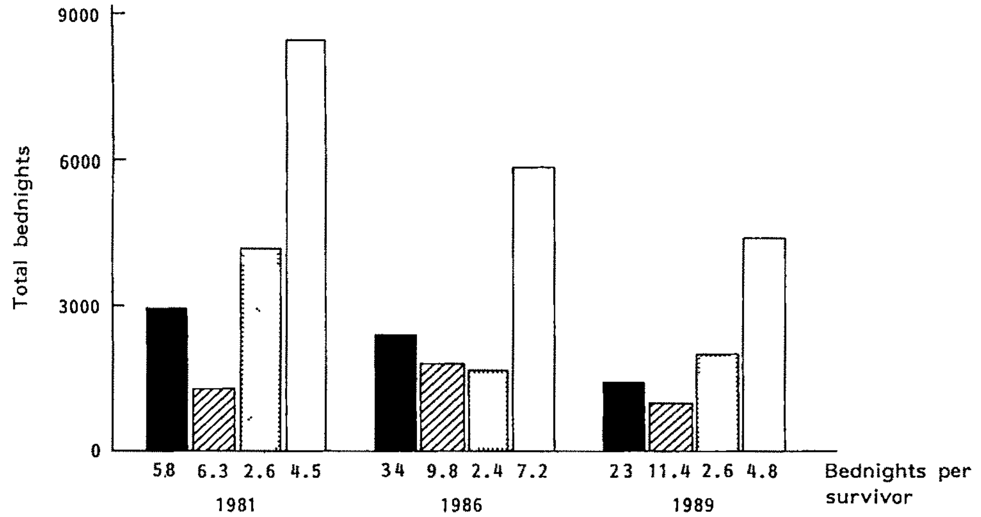

**Figure 2** *Total bednights occupied and bednights occupied per surviving patient* ■, *Severe,* ▨, *moderate,* □, *minor,* □, *total*

of bednights occupied per surviving patient with severe head injury fell from 58 in 1981 to 23 in 1989, while there was a small increase in this index in patients with moderate head injury

*Referral pattern of head-injured patients*

The proportion of patients with severe head injury referred from other hospitals remained constant. After 1981 the number of minor head injuries directly admitted from the accident and emergency department was reduced with a consequent increase in the proportion of referred cases of minor head injury (*Table 1*). The percentage of head-injured patients with other injuries remained high (*Table 2*). The prevalence of arterial hypotension (systolic blood pressure <90 mmHg) present on arrival in severely head-injured patients did not change significantly over the period of the study, being 15 per cent (14 of 93), 14 per cent (16 of 113) and 8 per cent (8 of 96) in 1981, 1986 and 1989 respectively.

**Table 1** *Source of referral of head injury admissions*

| | 1981 | 1986 | 1989 |
|---|---|---|---|
| Severe | | | |
| Direct | 49 (53) | 51 (45) | 49 (51) |
| Other hospital/GP | 44 (47) | 62 (55) | 47 (49) |
| Total | 93 | 113 | 96 |
| Moderate | | | |
| Direct | 163 (78) | 109 (56) | 43 (48) |
| Other hospital/GP | 47 (22) | 84 (44)* | 46 (52)† |
| Total | 210 | 193 | 89 |
| Minor | | | |
| Direct | 1413 (87) | 520 (74) | 530 (69) |
| Other hospital/GP | 203 (13) | 182 (26)‡ | 240 (31)§ |
| Total | 1616 | 702 | 770 |

Values in parentheses are percentages. *$P < 0{\cdot}001$ (1986 *versus* 1981, $\chi^2 = 19{\cdot}54$), †$P < 0{\cdot}001$ (1989 *versus* 1981, $\chi^2 = 23{\cdot}70$); ‡$P < 0{\cdot}001$ (1986 *versus* 1981, $\chi^2 = 164{\cdot}93$); §$P < 0{\cdot}001$ (1989 *versus* 1981, $\chi^2 = 118{\cdot}19$), §$P < 0{\cdot}05$ (1989 *versus* 1986, $\chi^2 = 4{\cdot}68$)

*Skull fracture*

The proportion of patients with skull fracture was greatest in severe head injury and least in minor head injury. The absolute number of skull fractures was greatest in cases of minor head injury (*Table 3*). This included the majority of depressed skull fractures. Of 91 patients with depressed skull fracture seen in the 3 years of the study, 67 (74 per cent) were scored at 13–15 points on the Glasgow Coma Scale and accord with previous experience[15].

### *CT scanning*

The proportion of cases of severe head injury undergoing CT rose from 77 per cent in 1981 to 88 per cent in 1986 and 1989 but there was a relatively greater increase in the CT scan rate in cases of moderate and minor injury (*Table 3*). The number of patients in whom repeat CT was employed did not change significantly, averaging 34 per cent of severe, 22 per cent of moderate and 11 per cent of minor head injuries.

### *Skull fracture, intracranial haematoma and injury severity*

The change to a more liberal CT scanning policy resulted in detection of an increased number of haematomas, from 72 in 1981 to 89 in 1986 and 100 in 1989 (*Table 3*). There was a shift in the proportion of haematomas detected in non-comatose patients from 42 per cent in 1981 to 58 per cent and 62 per cent in 1986 and 1989 More intracranial haematomas were detected but a number of these were small, without significant brain shift and did not require evacuation. This proportion increased from 24 per cent in 1981, to 38 per cent in 1986 and to 54 per cent in 1989. The number treated by surgical evacuation has been constant (*Table 3*). Of those operated on the proportion of non-comatose patients increased significantly from 38 per cent in 1981 to 60 per cent in 1986 and 54 per cent in 1989. The odds of detecting and operating on a non-comatose patient with an intracranial haematoma doubled in 1986/1989 compared with 1981 (*Figure 3*)

### *Intensive therapy*

Over the study period there was an increase in the use of artificial ventilation in patients with severe (comatose) injury from 57 per cent in 1981 to 77 per cent and 82 per cent in 1986 and 1989. The use of intracranial pressure monitoring increased from 35 per cent to 49 per cent of cases

### *Early outcome from injury*

In 1981 early mortality rates (defined at 1 month or at discharge) in cases of severe, moderate and minor head injury were 45 per cent, 3·8 per cent and 0·4 per cent respectively (*Table 4*). By 1989, mortality had fallen across the board but the reductions did not reach statistical significance. Because of the large number of direct admissions to the unit, a relatively large number of our patients were elderly (12 per cent over 70 years) These patients accounted for about a third of all deaths in the series, and their poor outcome did not change significantly during this study

The proportion of severely injured patients making a

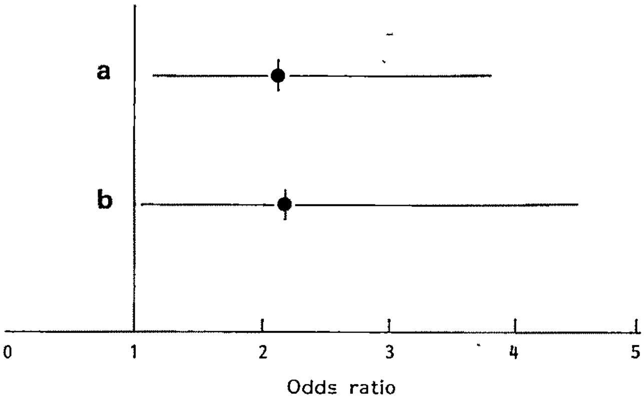

**Figure 3** *Effect of change in computed tomography scanning policy on pattern of intracranial haematomas detected and operated on Values are odds ratios with 95 per cent confidence interval* **a** *odds of an intracranial haematoma being detected in a non-comatose patient in 1986/1989 as compared with 1981,* **b** *odds of an intracranial haematoma being operated on in a non-comatose patient in 1986/1989 as compared with 1981*

**Table 4** *Early mortality rates from head injury in patients according to age*

| | 1981 | | 1986 | | 1989 | |
|---|---|---|---|---|---|---|
| | *n* | Deaths | *n* | Deaths | *n* | Deaths |
| Severe | | | | | | |
| ≤70 years | 83 | 33 (40) | 103 | 35 (34) | 83 | 23 (28) |
| >70 years | 10 | 9 (90) | 10 | 8 (80) | 13 | 10 (77) |
| Total | 93 | 42 (45) | 113 | 43 (38) | 96 | 33 (34) |
| Moderate | | | | | | |
| ≤70 years | 187 | 2 (2·3) | 165 | 1 (0·6) | 74 | 0 (0) |
| >70 years | 23 | 6 (26) | 28 | 8 (29) | 15 | 2 (13) |
| Total | 210 | 8 (3·8) | 193 | 9 (4·7) | 89 | 2 (2·2) |
| Minor | | | | | | |
| ≤70 years | 1449 | 4 (0·3) | 611 | 2 (0·3) | 646 | 0 (0) |
| >70 years | 167 | 3 (1·8) | 91 | 2 (2·2) | 124 | 3 (2·4) |
| Total | 1616 | 7 (0·4) | 702 | 4 (0·6) | 770 | 3 (0·4) |
| Total | | | | | | |
| ≤70 years | 1719 | 39 (2·3) | 879 | 38 (4·3) | 803 | 15 (1·9) |
| >70 years | 200 | 18 (9·0) | 129 | 18 (14) | 152 | 23 (15) |
| Grand total | 1919 | 57 (3·0) | 1008 | 56 (5·6) | 955 | 38 (4·0) |

Values in parentheses are percentages

**Table 2** *Numbers of patients with associated injuries*

| | 1981 | 1986 | 1989 |
|---|---|---|---|
| Severe | 51 of 93 (55) | 72 of 113 (64) | 66 of 96 (69) |
| Moderate | 55 of 210 (26) | 84 of 193 (44)* | 44 of 89 (49)† |
| Minor | 403 of 1616 (25) | 294 of 702 (42)‡ | 297 of 770 (39)§ |

Values in parentheses are percentages *$P < 0·001$ (1986 *versus* 1981, $\chi^2 = 12·61$), †$P < 0·001$ (1989 *versus* 1981, $\chi^2 = 14·22$); ‡$P < 0·001$ (1986 *versus* 1981, $\chi^2 = 66·00$), §$P < 0·001$ (1989 *versus* 1981, $\chi^2 = 48·76$)

**Table 3** *Detection of intracranial haematoma*

| | 1981 | | 1986 | | 1989 | |
|---|---|---|---|---|---|---|
| | Severe | Moderate/ minor | Severe | Moderate/ minor | Severe | Moderate/ minor |
| Patients with head injury | 93 | 1826 | 113 | 895 | 96 | 859 |
| Patients with skull fracture | 56 (60) | 217 (12) | 55 (49) | 191 (21) | 58 (60) | 185 (21) |
| Patients undergoing computed tomography | 72 (77) | 109 (6) | 99 (88) | 227 (25)* | 85 (88) | 223 (26)† |
| Patients in whom haematomas detected | 42 (45) | 30 (2) | 37 (33) | 52 (6) | 38 (40) | 62 (7)‡ |
| Patients with haematomas operated on | 34 (37) | 21 (1) | 22 (19) | 33 (4)§ | 21 (22) | 25 (3) |

Values in parentheses are percentages. *$P < 0·001$ (1986 *versus* 1981, $\chi^2 = 206·93$), †$P < 0·001$ (1989 *versus* 1981, $\chi^2 = 213·61$); ‡$P < 0·02$ (1989 *versus* 1981, $\chi^2 = 6·16$); §$P < 0·05$ (1986 *versus* 1981, $\chi^2 = 4·40$)

recovery to independent status by the time of discharge (good recovery and moderate disability on the Glasgow Outcome Scale) has risen from 19 per cent in 1981 to 40 per cent in 1986 ($\chi^2 = 9\cdot3$, $P < 0\cdot01$) and to 45 per cent in 1989 ($\chi^2 = 12\cdot85$, $P < 0\cdot001$).

## Discussion

There has been a large reduction in the number of head injury admissions. The greatest contribution to this was adoption of revised guidelines for admission. The introduction of seat belt legislation resulted in only a 5 per cent reduction in the admission rate because in Edinburgh, a large proportion of road traffic-related head injuries occur in pedestrians[12].

Making CT more readily available resulted in detection of increased numbers of intracranial haematomas in this series and others[2,10,16–21]. A greater proportion of haematomas that, on account of size and associated brain shift, require operative removal has been detected in non-comatose patients. More haematomas were detected that were deemed not to require surgical evacuation[13,20]. Non-operative management of an extradural or intradural haematoma entails the closest of clinical supervision, may require continuous monitoring of intracranial pressure and always results in repeated CT scans[22,23]. Miller and colleagues[10] found that 17 per cent of their total series of 1080 patients operated on for haematoma had an admission GCS of 15 points. Knuckey *et al.*[19] recently reported that 7 of 22 (32 per cent) patients found to be harbouring an extradural haematoma while still asymptomatic subsequently deteriorated and needed urgent surgery. Non-operative management of intracranial haematoma, therefore, should always be conducted in, or close to, a neurosurgical service.

Guidelines for the employment of CT facilities in general hospitals without a unit for head-injured patients become important. Servadei *et al.*[18] support the use of such facilities but recommend transfer of comatose patients to the neurosurgical unit with CT performed there. Jennett and Macpherson[24] provided guidelines for CT at first hospital and transfer to the neurosurgical unit.

A criticism of intensive therapy for patients with head injury is that a reduction in mortality will be balanced by an increase in the proportion of severely disabled or vegetative survivors. This has repeatedly been shown to be untrue[25–28]. This study presents more evidence in favour of an intensive pre-emptive approach to management. Had reduced mortality led to prolonged survival in a vegetative state, the index of bednights per surviving patient with severe head injury would have increased. There was a major reduction in bednights occupied, despite the fact that the discharge policy from the unit was unaltered. The higher incidence in 1986 and 1989 of other injuries in patients with moderate head injury may explain the increase in bednights occupied per survivor in these cases.

There is an association between arterial hypotension and multiple injury in severely head-injured patients, and hypotension is an important prognostic factor in head injury mortality[26]. The lack of signficant change in the incidence of arterial hypotension over the period of this study suggests that changes in patient outcome could not be explained by differences in the patient population or in prehospital care.

In an important study, Klauber and colleagues[29] compared outcomes in 7912 cases of head injury of all degrees of severity treated in 41 hospitals in three cities in the USA. Considerable variation in outcome was recorded in different hospitals, from 43 per cent below to 52 per cent above the expected mortality rate, based on the distribution of known mortality risk factors. These differences were largely accounted for by variations in outcome in those patients who had a low *a priori* risk of death, and not in the high-risk group of patients. There does, therefore, seem to be a compelling argument for providing neurosurgical assessment and supervision for less severely head-injured patients as well as for comatose patients. The high prevalence of multiple injury in patients with moderate and minor head injury confirms the need to locate a regional head injury centre close to the regional trauma service with expertise in resuscitation and safe transport.

There was a large reduction in total occupied bednights during this study. Despite a reduction from 23 to 18 beds in the head injury unit after 1986, there was a fall in bed occupancy rate from 96 per cent in 1981 to 64 per cent in 1989. The index of bednights used per surviving patient represents an attempt to measure efficiency, as it takes account of the mortality rate in each category of head injury and the length of stay in the head injury unit. The most striking reduction applied to severely head-injured patients, the most costly to manage.

Based on this study a regional head injury service would require 2–4 intensive care beds and 6–12 other beds per million of the referral population, in addition to those beds already provided for the regional neurosurgical service. Facilities for CT, artificial ventilation and intracranial pressure monitoring should be available. These arrangements are feasible in many parts of the UK. If implemented they should produce improvements in the management of head injury.

## Acknowledgements

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# Early cardiorespiratory findings after severe blunt thoracic trauma and their relation to outcome

*This study examined the initial haemodynamic and oxygen transport patterns in 24 patients with severe blunt thoracic trauma in whom immediate monitoring with femoral and pulmonary artery catheters was required after admission to the intensive care unit. All patients required mechanical ventilation and were studied before receiving inhalational anaesthesia and within 12 h of injury. Two groups of patients were identified; nine patients (group 1) had an impaired left ventricular stroke work index (LVSWI) and 15 patients had a normal LVSWI (group 2). There were no significant differences in the abbreviated injury scale score for the chest, the total injury severity score, or the mean ages of the two groups. There were significant differences in stroke volume index, 32* versus *56 ml* $m^{-2}$ ($P < 0{\cdot}001$), *and cardiac index, 3·2* versus *5·3 l* $min^{-1}\,m^{-2}$ ($P < 0{\cdot}001$), *and therefore in oxygen delivery, 469* versus *852 ml* $min^{-1}\,m^{-2}$ ($P < 0{\cdot}001$), *despite apparently adequate volume expansion using the same protocol and clinical criteria in both groups. Oxygen consumption was not significantly different in the two groups, 135* versus *157 ml* $min^{-1}\,m^{-2}$*, because of a higher oxygen extraction ratio in group 1, 29* versus *19 per cent* ($P < 0{\cdot}001$)*, and hence lower mixed venous oxygen saturation, 73* versus *82 per cent* ($P < 0{\cdot}02$)*. Seven patients in group 1 died (78 per cent) compared with two in group 2 (13 per cent). Early depression of cardiac function is associated with poor outcome in patients with thoracic trauma, and measurements of oxygen transport variables may influence resuscitation and the timing of surgical procedures.*

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Oxygen transport patterns have been shown to predict outcome in high-risk surgical patients[1–5] and maintenance of supranormal values of oxygen delivery has been shown to improve the survival rate in this group in two prospective clinical studies[6,7] These studies, however, included few patients with blunt thoracic trauma.

Death following trauma occurs at three stages: immediately at the scene of injury, at an intermediate phase during the early hours of hospital admissions and later at an interval of days or weeks, usually because of multisystem organ failure on the intensive care unit[8]. Two important identifiable types of organ failure that influence outcome are the adult respiratory distress syndrome (ARDS) and acute renal failure[9]. In a heterogeneous group of patients with haemorrhage and trauma studied after operation, lower values of cardiac index and oxygen delivery in the early phases predicted a higher incidence of ARDS and a worse outcome[10,11] Severe thoracic trauma could lower oxygen delivery by a combination of pulmonary and cardiac injury which could be compounded by loss of blood and circulating plasma volume due to associated injuries. In a previous study of patients with multiple trauma, it was demonstrated that oxygen consumption was maintained at high normal values in the absence of hypothermia in the early stages following injury[12]. In retrospect, three of four non-survivors in that study had low levels of oxygen delivery with predominant chest injuries This prompted the current prospective study of patients referred for intensive care with major chest injuries resulting from blunt trauma

## Patients and methods

Twenty-four consecutive patients admitted to the intensive care unit following severe blunt chest trauma, defined as an abbreviated injury scale value for the chest of more than three[13], were studied over a period of 30 months. Only patients who required femoral and pulmonary artery catheterization before any definitive surgery had been performed or administration of inhalational anaesthesia and who were within 12 h of receiving their injury were included. The mean time interval between injury and measurements was 3·2 h Patients were excluded if they had penetrating injuries, any evidence of previous pulmonary or cardiac disease, greater than 5 per cent full-thickness cutaneous burns or smoke inhalation, if they had received exogenous catecholamines before measurement of oxygen transport variables or had a central temperature of less than 36°C or more than 38°C Resuscitation was initiated in the emergency room according to a standard protocol which entailed endotracheal intubation, mechanical ventilation with supplemental inspired oxygen to maintain arterial oxyhaemoglobin saturation at more than 95 per cent, volume replacement with artificial colloid (modified fluid gelatin) and blood as clinically indicated. This was followed on the intensive care unit by controlled plasma volume expansion guided by measurements of pulmonary artery wedge pressure, stroke volume index (SVI) and urine output. After completion of volume replacement, measurements of heart rate, central venous pressure, wedge pressure, mean systemic arterial pressure and cardiac output were recorded (Marquette 7000 series bedside monitors, Milwaukee, Wisconsin, USA) Cardiac output was measured by thermodilution using cooled injectate (temperature <10°C) with display of the thermodilution curve. The mean of three successive measurements within 5 per cent of each other and with satisfactory curves was recorded. Simultaneous samples of arterial and mixed venous blood were taken for measurement of haemoglobin, arterial and mixed venous partial pressure of oxygen, and arterial and mixed venous oxyhaemoglobin saturation. The patient's height and weight were measured for calculation of body surface area. Cardiac index, SVI, arterial and mixed venous oxygen content, oxygen delivery and consumption, and oxygen extraction ratio were calculated using standard formulae[2]. Left ventricular stroke work index (LVSWI) was calculated from the formula

$$\mathrm{LVSWI} = \mathrm{SVI} \times (\text{mean arterial pressure} - \text{wedge pressure}) \times 0{\cdot}0136\ \mathrm{g\ m\ m^{-2}}$$

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All the results given are the first measurements taken after completion of volume expansion as defined above.

The development of ARDS was noted. This was defined as severe respiratory failure with a pulmonary shunt fraction greater than 30 per cent, wedge pressure of less than 18 mmHg and diffuse bilateral pulmonary infiltrates on chest radiography. Acute renal failure was defined as a urine output of less than 0·5 ml kg$^{-1}$ h$^{-1}$ for at least 24 h, with plasma creatinine rising to more than 400 μmol l$^{-1}$ and the need for haemodialysis. Autopsy was performed on all non-survivors and the results noted. The abbreviated injury scale values obtained for the chest and other injured regions were utilized at hospital discharge or death to calculate the injury severity score for each patient[13]. Haemodynamic and oxygen transport variables were normally distributed and were therefore analysed with Student's paired *t* test. The incidence of ARDS, acute renal failure and mortality in the two groups was analysed using the $\chi^2$ test. Statistical significance was considered at a *P* value of less than 0·05.

## Results

Two groups of patients were identified on the basis of the maximal level of LVSWI achieved immediately after controlled plasma volume expansion in the intensive care unit. Nine patients (group 1) had low levels of LVSWI (<44 g m m$^{-2}$). Fifteen patients (group 2) had normal values of LVSWI (>44 g m m$^{-2}$). There was no difference in age, abbreviated injury scale score for the chest and total injury severity score between the two groups (*Table 1*) or in the distribution of associated injuries (*Table 2*). There were no differences in heart rate, central venous pressure, wedge pressure, pulmonary shunt fraction or arterial oxygen saturation between the two groups (*Table 3*). Group 1 had a lower cardiac index, SVI and haemoglobin concentration, and therefore oxygen delivery (*Figures 1* and *2*, *Table 4*). Group 1 maintained oxygen consumption by means of a higher oxygen extraction ratio and lower mixed venous oxygen saturation (*Figure 2*, *Table 4*). All patients in group 1 and eight in group 2 developed ARDS (*Table 1*). Three patients in group 1 but none in group 2 developed acute renal failure. Seven patients in group 1 (78 per cent) and two in group 2 (13 per cent) died from complications of multiple organ failure on the intensive care unit. Of the seven patients who died in group 1 (*Table 1*), autopsy revealed evidence of definite but not extensive cardiac contusion in five.

**Table 1** *Patient characteristics*

| | Group 1 (*n* = 9) | Group 2 (*n* = 15) | *P** |
|---|---|---|---|
| Age (years) | 46(25) | 35(17) | n.s. |
| Chest AIS | 4(0·5) | 4(0·6) | n.s. |
| Total injury severity score | 32(13) | 26(8) | n.s. |
| ARDS | 9 | 8 | <0·05 |
| Acute renal failure | 3 | 0 | <0·05 |
| No. of deaths | 7 | 2 | <0·05 |

Values are mean(s.d.). Chest AIS, abbreviated injury scale score for the chest; ARDS, adult respiratory distress syndrome, n.s., not significant, *$\chi^2$ test

**Table 2** *Associated abdominal, craniospinal and limb injuries*

| | Group 1 | | Group 2 | |
|---|---|---|---|---|
| Injury | *n* | Mean AIS | *n* | Mean AIS |
| Abdominal | 5 | 3 | 7 | 3 |
| Craniospinal | 5 | 4 | 8 | 3 |
| Limb | 9 | 3 | 10 | 3 |

Values are the number of patients with injuries and the mean abbreviated injury scale (AIS) score[13] for body regions

**Table 3** *Haemodynamic data for groups 1 and 2 following controlled plasma volume expansion with modified fluid gelatin and blood*

| | Group 1 | Group 2 | *P** |
|---|---|---|---|
| Heart rate (beats min$^{-1}$) | 102(23) | 94(18) | n.s. |
| Mean arterial pressure (mmHg) | 82(9) | 95(15) | n.s. |
| Central venous pressure (mmHg) | 11(4) | 11(5) | n.s. |
| Wedge pressure (mmHg) | 14(7) | 13(4) | n.s. |
| LVSWI (g m m$^{-2}$) | 30(10) | 62(14) | <0·001 |

Values are mean(s.d.). LVSWI, left ventricular stroke work index, n.s., not significant, *Student's paired *t* test

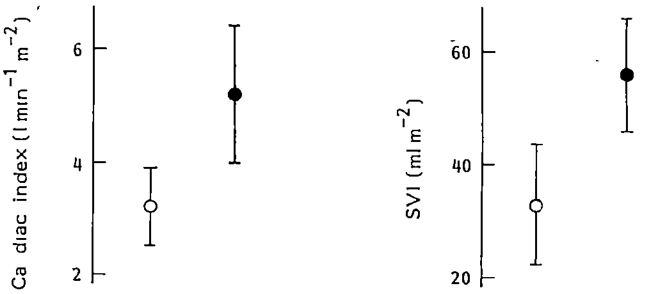

**Figure 1** *Levels of cardiac index and stroke volume index (SVI) in group 1 (○) and group 2 (●).* P < *0·001 for difference between the groups for both indices (Student's paired* t *test)*

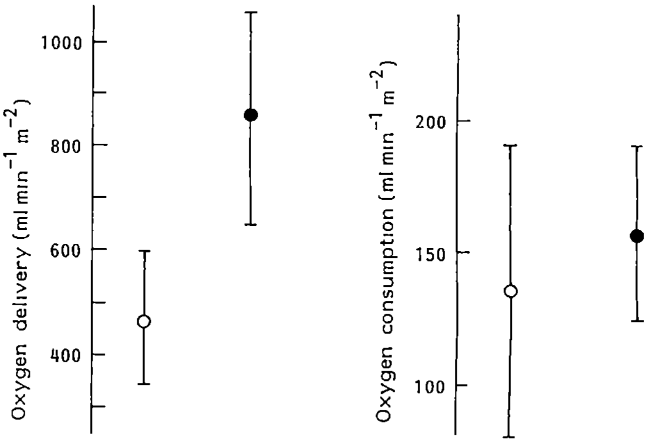

**Figure 2** *Levels of oxygen delivery and consumption in group 1 (○) and group 2 (●).* P < *0·001 for oxygen delivery; there was no significant difference between the groups for oxygen consumption (Student's paired* t *test)*

**Table 4** *Oxygen transport data for groups 1 and 2 after controlled plasma volume expansion with modified fluid gelatin and blood*

| | Group 1 | Group 2 | *P** |
|---|---|---|---|
| Haemoglobin (g dl$^{-1}$) | 10·3(0·7) | 12·1(1·7) | <0·001 |
| Oxygen extraction ratio (%) | 29(11) | 19(6) | <0·001 |
| $S_{vO_2}$ (%) | 73(14) | 82(5) | <0·02 |
| $Q_s/Q_t$ (%) | 19(4) | 22(11) | n.s. |

Values are mean(s.d.). $S_{vO_2}$, mixed venous oxygen saturation, $Q_s/Q_t$, pulmonary venous admixture, n.s., not significant, *Student's paired *t* test

## Discussion

LVSWI was used to separate patients in this study into two groups for four reasons.

1. Previous studies of perioperative patients have shown that the maximal LVSWI achieved early in critical illness seemed to correlate with outcome[2–4].

2. Calculations of LVSWI from data provided in two other studies of patients with haemorrhage and trauma indicated a strong prognostic correlation with this variable[10,14]
3. In a previous study we retrospectively identified a group of patients with poor prognosis having low LVSWI following chest injury and associated with high oxygen extraction ratio and low mixed venous oxygen saturation in the face of inadequate oxygen delivery[12].
4. Because the calculation of LVSWI includes measurements of afterload and preload it is a measure of cardiac mechanical work and performance.

There was no significant difference in wedge pressure between the two groups, so it is unlikely that the difference in SVI was due to gross differences in preload and in volume loading relative to needs. Volume expansion was controlled and guided by frequent measurements of pulmonary artery wedge pressure in both groups. A criticism of the current study is that owing to the rapid rate of resuscitation at several sites (prehospital, emergency room, operating room and intensive care unit) an accurate estimate of the volumes of colloid and blood administered was not available. Although LVSWI was chosen in advance for the reasons emphasized above, the level of stroke volume recorded clearly identifies the two groups (*Figure 1*) and the use of this variable would not have affected the results.

Until recently, oxygen consumption after trauma has been said to be biphasic with an initial low level or 'ebb' phase merging after 24–48 h into a so-called 'flow' phase of increased oxygen consumption[15]. This has recently been disputed[12]. Looking specifically at blunt thoracic trauma these results confirm that oxygen consumption, in the absence of hypothermia, is normal or high in the majority of patients when measured soon after injury. Evidence of an inadequate oxygen delivery in a significant number of patients with chest injuries in the current study is revealed by the higher levels of oxygen extraction ratio and lower levels of mixed venous oxygen saturation in a group with a much higher incidence of organ failure and death despite a similar age and severity and type of injuries. The lower levels of oxygen delivery in this group were related largely to a reduction in SVI but were contributed to by a lower level of haemoglobin and thereby arterial oxygen content. This has important implications for therapy as it is rather unfortunate that the group with worse cardiac function was relatively undertransfused with blood compared with the group with high cardiac output, although right and left ventricular filling pressures in each group were comparable. Before correction of hypoxia, volume expansion and blood transfusion, it could be presumed that the levels of oxygen delivery in both groups of patients, but especially those in group 1, would have been even lower. The severity of the early lung injury (judged by the level of pulmonary shunt fraction and requirements for high inspired oxygen concentrations) was no different between the two groups. The degree of pulmonary venous admixture has recently been shown to be the most accurate way of quantifying lung injury after surgery and trauma[16]. After hospital admission, assuming adequate surgical management of injuries, causes of death after blunt trauma have been shown to be related to the onset of multiple system organ failure, especially ARDS and acute renal failure[17,18]. In the perioperative studies of Shoemaker *et al.*[3,9], these complications were shown to be correlated with lower levels of oxygen delivery. A similar correlation is shown in the present study. Obvious objective explanations for the impaired stroke volume were found at post mortem in five patients, and this is now recognized to be a common complication of blunt chest injury[19]. In its severest form this can present with clinical cardiogenic shock, sometimes with evidence of mechanical valvular dysfunction. The levels of cardiac index in group 1 patients were not comparable to those found in cardiogenic shock[20] and were within the normal range in most. These normal values were not sufficient to maintain tissue oxygenation in the face of increased demands, and contributed to organ failure and death despite apparent adequate resuscitation based on measurements of heart rate, mean arterial pressure, central venous and wedge pressure. Optimal levels of cardiac index were achieved eventually in all of these cases except one, but only after a delay of several hours before optimal inotropic support was established. The explanation of inadequate cardiac output in the other two patients in group 1 is rather speculative. One patient achieved an adequate cardiac output, despite use of inotropes, only following the removal of a crushed kidney, and a second responded only when a crushed non-viable upper limb was amputated It seems probable that these two patients, who had no post-mortem evidence of cardiac contusion, were suffering from the effects of circulating myocardial depressant factors arising from damaged tissues[21].

In conclusion, patients with severe blunt thoracic trauma, especially when associated with extrathoracic injuries and with poor outcome, have depressed myocardial function which contributes to an inadequate oxygen delivery such that a normal or high oxygen consumption is maintained by increases in the oxygen extraction ratio and decreases in mixed venous oxygen saturation. Early left ventricular dysfunction is a marker of a higher incidence of mortality and morbidity as shown by ARDS and acute renal failure. This tissue hypoxia is not revealed by monitoring of heart rate, central venous pressure, mean arterial pressure or wedge pressure In such patients particular attention should be paid to titration of blood transfusion and to the introduction of inotropic support.

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# Effect of transforming growth factor beta and basic fibroblast growth factor on steroid-impaired healing intestinal wounds

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*A longitudinal intestinal wound model in the pig was used to assess the effect of parenteral steroids (betamethasone $12\ \text{mg}\ 50\ \text{kg}^{-1}$ intramuscularly twice daily) on breaking load. Steroid treatment significantly decreased the breaking load of wounds in the ileum and colon in comparison with wounds from saline-treated animals. In a further group of animals receiving steroids, paired longitudinal wounds were constructed. One wound of a pair was treated with a local application of transforming growth factor beta (TGF-β) (5 μg per wound) or basic fibroblast growth factor (5 μg per wound) in a collagen suspension. The other wound was treated with a collagen suspension alone. Ileal wounds treated with TGF-β were significantly stronger than collagen-treated controls at 7 days. The steroid-induced impairment of breaking load in intestinal wounds is partially reversed by a local application of TGF-β in a collagen suspension at the time of surgery.*

Peptide growth factors are increasingly implicated in the control of wound healing[1]. Recombinant biotechnology provides amounts of these previously rare peptides which allows their use in *in vivo* experiments and may permit their clinical use. Epidermal growth factor[2], tumour necrosis factor[3], transforming growth factor beta (TGF-β)[4] and platelet-derived growth factor[5], applied in slow release suspensions or vehicles to healing incisional skin wounds at the time of wounding, accelerate the gain in breaking load of these wounds. Mustoe and colleagues[6] recently demonstrated acceleration of the gain in strength of healing rabbit gastrotomy wounds with topical TGF-β in a collagen suspension. Local applications of peptide can be shown to reverse the deleterious effects of steroid therapy[7], cytotoxic treatment[8] and local radiotherapy[9] in simple skin incisional wound models. It remains unclear to what extent these various effects are organ- or species-specific.

The failure of intestinal wounds is associated with considerable morbidity and mortality rates and usually occurs in situations of impaired healing. Steroid impairment of cutaneous healing is well documented[10,11]. Few studies of the effects of steroids on healing intestinal wounds have been published[12,13]. One recent experimental study failed to demonstrate impairment of healing following steroid treatment[14]. Clinical studies have failed to demonstrate any deleterious effects on intestinal healing. The numbers of treated patients in any particular trial would, however, be small and demonstrating any negative effect would be difficult[15]. The effect of steroid therapy on healing longitudinal enterotomy wounds in pigs was assessed by measurement of breaking load The effect of local applications of two peptide growth factors, TGF-β and basic fibroblast growth factor (bFGF), each in a collagen suspension, was tested on the steroid-impaired healing of enterotomy wounds.

## Materials and methods

Weanling Landrace pigs weighing between 16 and 25 kg were used throughout. Pigs were housed in groups of up to four and maintained on a constant day/night cycle. Animals were weighed 48 h before the operation, at the time of operation and when killed

An intramuscular betamethasone preparation (Betsolan®, Coopers Pittman/Moore, Crewe, UK) was used. Biological activity of TGF-$\beta_1$ and bFGF was ensured by a simple *in vivo* assay utilizing Swiss 3T3 fibroblasts between the tenth and 14th passage grown to confluence in 96-well plates Mitogenicity was assessed by uptake of tritiated thymidine The vehicle used for delivery of peptide was 200 μl of a dilute collagen suspension (Zyderm II; Collagen Corporation, Palo Alto, California, USA) to provide a viscous preparation allowing easy application to wound edges that may delay release of peptide for a short period at a site of local application[5].

### *Demonstration of steroid impairment of healing*

One group of seven pigs was treated with betamethasone $12\ \text{mg}\ 50\ \text{kg}^{-1}$ intramuscularly twice daily, beginning 48 h before the operation and continuing until killing. Seven other animals received a similar volume of saline intramuscularly At operation animals had 6 cm antimesenteric enterotomy wounds constructed at standard sites (three in the ileum and two in the colon) and were killed at 7 days Statistical comparisons were between wounds in steroid- and saline-treated animals.

### *Effect of growth factors*

A further 19 pigs were treated with betamethasone $12\ \text{mg}\ 50\ \text{kg}^{-1}$ intramuscularly twice a day beginning 48 h before the operation and continuing until killing Animals had paired wounds constructed at standard sites, three pairs in the ileum and one in the colon (*Figure 1*). Each member of a pair was 30 cm from its partner. One wound in a pair was treated with growth factor in a collagen suspension, the other was treated with collagen suspension alone. All control wounds in a particular animal were completed before growth factor-treated wounds to prevent contamination. A standard wounding protocol was followed; the seromuscular layer was divided with cutting diathermy until the mucosa bulged, and growth factor or control solution was applied to the wound to allow even application to the whole surface. The mucosa was then opened with a blade before suture. Animals were treated with only one growth factor. In six animals the effects of saline were compared with collagen suspension. In nine animals the effects of TGF-β (5 μg) in a collagen suspension were compared with collagen and in four animals the effects of bFGF (5 μg) in a collagen suspension were compared with collagen Statistical comparisons were between paired wounds

### *Wounding model*

Fluids only were allowed for the 12 h preceding operation Anaesthesia was induced with halothane and maintained after intubation with a mixture of halothane, nitrous oxide and oxygen A single dose of penicillin (Triplopen®, Glaxo, Greenford, UK) was given with induction

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*Paper presented at the meeting of the Surgical Research Society held in Lancaster, UK on 4–5 July 1991*

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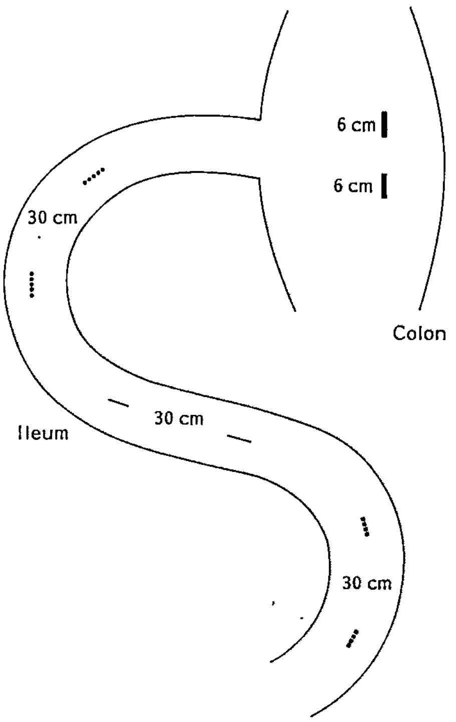

**Figure 1** *Distribution of wounds in growth factor-treated animals three pairs in the ileum and one pair in the colon*

Wounds were sutured at 4 mm intervals with interrupted 3/0 seromuscular polyglactin 910 (Vicryl®; Ethicon Ltd, Edinburgh, UK) Fluids were allowed immediately after recovery and a liquid diet was gradually introduced Animals were killed at 7 days The intestine was removed immediately for testing and kept on ice until this was completed Wounds were tested beginning proximally and continuing distally Sutures were removed and a 2-cm ring of bowel containing the enterotomy wound was cut A tensiometer (model TTBM A0543, Instrom Corporation, Canton, Massachusetts, USA) was adapted so that hooks were used rather than the more traditional clamps[16]. The hooks were inserted into the lumen of each segment. The upper crosshead was fixed and connected to a load cell; the lower crosshead moved at a constant strain Each specimen was tested to disruption A crosshead speed of 1 cm min$^{-1}$ was used for the initial group of animals used to demonstrate steroid impairment of healing. In order to shorten the testing period the crosshead speed was increased to 5 cm min$^{-1}$ with growth factor-treated animals A load deformation curve was produced on a chart recorder from which the breaking load of each specimen was calculated Breaking loads are expressed as g cm$^{-1}$

### *Histology*

The remainder of the wound was fixed in 10 per cent formal saline for 48 h, processed and then orientated accurately in paraffin wax before embedding. Sections, 5 $\mu$m thick, were cut and stained with haematoxylin and eosin or a van Gieson stain (for collagen). A single pathologist who was unaware of the identity of individual slides then examined each section

### *Statistics*

Results are expressed as mean(s e m ) unless otherwise stated All statistical comparisons are with non-parametric tests, a Wilcoxon rank sum test for unpaired data and a Wilcoxon signed rank test for paired data

## Results

### *Mortality rate*

Two animals were killed before 7 days; one had a volvulus of dilated proximal ileal loops but no intra-abdominal pathology was apparent in the other. A further six animals died before 7 days. Of these, one animal had peritonitis and no particular enterotomy could be implicated; the other five animals demonstrated dilation and necrosis or frank volvulus of proximal ileal loops.

### *Effects of steroids*

There were no significant changes in weight between the steroid- and saline-treated groups. It was common to find small intraperitoneal collections of fluid in steroid-treated animals. Steroid treatment significantly decreased the mean(s.e.m ) breaking load of ileal (160(20) g cm$^{-1}$ *versus* 320(32) g cm$^{-1}$) and colonic (200(12) g cm$^{-1}$ *versus* 390(33) g cm$^{-1}$) wounds (both $P < 0.01$, Wilcoxon rank sum test, *Table 1* and *Figure 2*). There were no differences in breaking load between the three different sites within the ileum or the two sites in the colon (*Table 1*). No histological differences were apparent at 7 days between steroid- and saline-treated animals

### *Effect of growth factors*

There were no significant differences in breaking load between collagen-treated wounds and saline controls (*Table 2*) Wounds treated with TGF-$\beta$ had increased mean(s.e m.) breaking loads (ileal 285(32) g cm$^{-1}$ *versus* 180(11) g cm$^{-1}$, colonic 365(59) g cm$^{-1}$ *versus* 260(40) g cm$^{-1}$) in comparison with collagen-treated controls (*Figure 3*). This was significant at the 5 per cent level for ileal wounds but just failed to reach significance with colonic wounds. No major differences were noted between wounds treated with TGF-$\beta$ and collagen-treated controls when histological sections were examined.

**Table 1** *Breaking strength of intestinal wounds in steroid- and saline-treated animals at specific sites in the ileum (A, B and C) and colon (D and E)*

| | Saline | Steroid |
|---|---|---|
| Ileum | | |
| Site A ($n = 6$) | 310(63) | 150(29) |
| Site B ($n = 6$) | 290(58) | 170(37) |
| Site C ($n = 6$) | 360(37) | 170(35) |
| Mean ($n = 18$) | 320(32) | 160(20)* |
| Colon | | |
| Site D ($n = 6$) | 370(49) | 210(28) |
| Site E ($n = 6$) | 415(40) | 185(14) |
| Mean ($n = 12$) | 390(33) | 200(12)* |

Values are mean(s.e.m.) expressed in g cm$^{-1}$ $n$, Number of wounds, *$P < 0.01$ (Wilcoxon rank sum test)

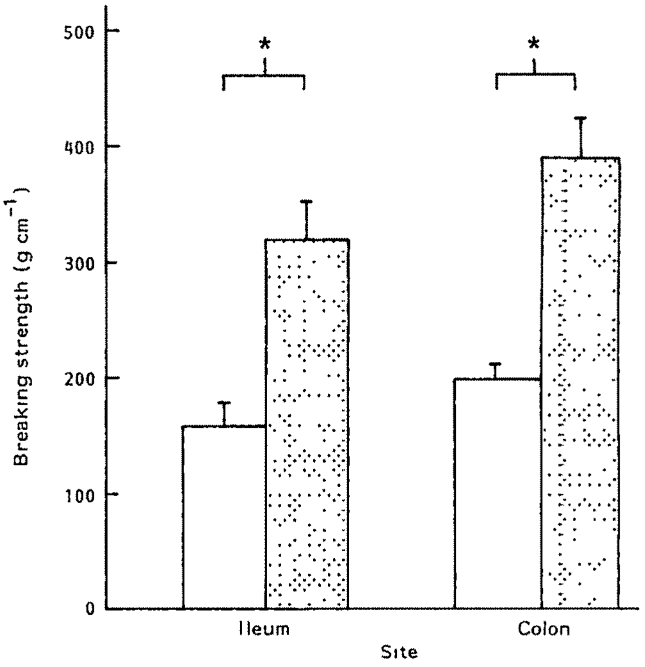

**Figure 2** *Breaking strength of enterotomy wounds in steroid- (□) and saline-treated (□) animals Values are mean(s e.m.) There were 18 ileal and 12 colonic wounds in each group.* *P < 0 01 (*Wilcoxon rank sum test*)

**Table 2** *Effect of locally applied growth factor on breaking strength*

| | Ileum | | Colon | |
|---|---|---|---|---|
| | Treated | Control | Treated | Control |
| TGF-β | 285(32) | 180(11)* | 365(59) | 260(40) |
| | (*n* = 18 pairs) | | (*n* = 6 pairs) | |
| bFGF | 145(19) | 200(21)* | 155(67) | 185(33) |
| | (*n* = 12 pairs) | | (*n* = 4 pairs) | |
| Collagen | 165(18) | 160(34) | 220(62) | 165(42) |
| | (*n* = 9 pairs) | | (*n* = 4 pairs) | |

Values are mean(s.e.m.) expressed in g $cm^{-1}$. *n*, Number of paired wounds; TGF-β, transforming growth factor beta; bFGF, basic fibroblast growth factor; $*P < 0.05$ (Wilcoxon signed rank test)

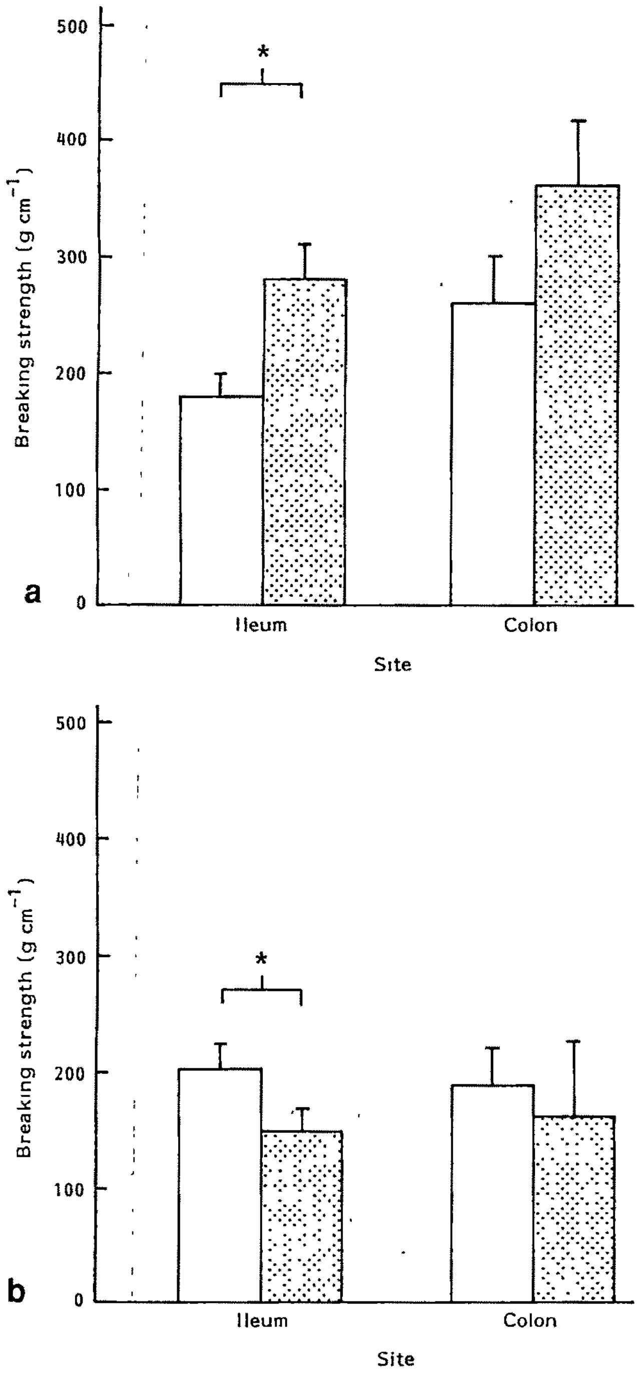

**Figure 3** *Breaking strength of paired treated (▨) and control (□) wounds in steroid-treated animals Values are mean(s.e.m.)* **a** *Transforming growth factor beta, 18 ileum pairs, six colon pairs* **b** *Basic fibroblast growth factor, 12 ileum pairs, four colon pairs* $*P < 0.05$ *(Wilcoxon signed rank test)*

Basic FGF-treated ileal wounds had significantly decreased breaking loads in comparison with collagen-treated control wounds (mean(s.e.m.) 145(19) g $cm^{-1}$ *versus* 200(21) g $cm^{-1}$, *Figure 3*). Examination of histological sections suggested that bFGF-treated wounds were more cellular than paired collagen-treated control wounds.

## Discussion

Wound healing in the intestine has traditionally been estimated by the measurement of anastomotic bursting strength A segment of bowel with an anastomosis at its centre is distended with fluid or gas and the pressure at which bursting occurs is taken as a measure of intestinal strength. Unfortunately, after the first few days of healing, disruption characteristically occurs away from the anastomosis; this is not a reflection of supranormal anastomotic wound strength but rather the decreased distensibility of the anastomotic area. The law of Laplace states that the tension in the wall of a distending tube is directly related to its diameter and the tension in the bowel wall distal and proximal to an anastomosis may greatly exceed that at the anastomotic line[17]. For this reason we and a number of others[18,19] have preferred to measure the breaking load of longitudinal enterotomy wounds or of segments of intestine containing an anastomosis. Collagen is responsible for the strength of a wound A parallel association has been demonstrated between collagen concentration and wound strength in healing rat gastrotomy incisions[20]. It seems reasonable to speculate, however, that the absolute amount of collagen within a wound and its quality and organization must be important factors.

Mastboom and colleagues recently failed to demonstrate any deleterious effect of steroid therapy (methylprednisolone 10 mg $kg^{-1}$ $day^{-1}$) in rats on the healing of intestinal anastomosis as assessed by bursting pressure[14] At 7 days, however, all the segments of bowel tested burst away from the anastomosis. We have demonstrated that steroid treatment (betamethasone 24 mg 50 $kg^{-1}$ $day^{-1}$) significantly decreases the breaking load of both ileal and colonic enterotomy wounds at 7 days.

Steroids might act at a number of points in a wound healing cascade to depress collagen synthesis Steroid treatment causes profound monocytopenia[21] Monocytes are now recognized as having a pivotal role within a wound healing cascade[22] Once present at a site of healing they release peptide growth factors that recruit further cells and stimulate collagen and matrix production *In vitro* steroids can be shown to have a direct effect on fibroblasts, decreasing messenger RNA transcript numbers for both procollagen and matrix protein[23,24]. Clinically a direct depression of both collagen and matrix production might be responsible for the deleterious effects of steroid therapy on fibroplasia

Basic FGF is ubiquitous and found throughout the body[25]. It has chemotactic and mitogenic effects predominantly on cells of mesenchymal origin (including fibroblasts). *In vitro* it is also chemotactic and mitogenic for endothelial cells[26] and in simple *in vivo* assays bFGF is a potent angiogenic factor[27]. These two attributes of bFGF – its mitogenic effect on fibroblasts and its angiogenic properties *in vivo* – suggest it is a critical factor involved in the formation of granulation tissue.

Injection of bFGF into simple wound chambers increases the cellularity of granulation tissue[28]. The infiltration of recombinant bFGF into healing rat incisional skin wounds on the third day after wounding increases the rate of gain of strength of treated wounds[29]. The inhibition of healing in diabetes shows some similarities to that seen with steroid therapy; bFGF increases the cellularity of treated sponges in diabetic rats[30]. Applications of bFGF in a collagen suspension to ileal enterotomy decreased the strength of treated incisions in comparison with collagen-treated controls at 7 days. Treated wounds appeared to be more cellular than control wounds We have since confirmed that simple applications of bFGF to healing skin wounds at the time of wounding may be detrimental to subsequent gain in wound strength[31]

TGF-β is found at its highest concentration in platelet α-granules[32]. It is released at a site of wounding and is chemotactic for both macrophages[33] and fibroblasts[34]. Macrophages recruited to a wound can be shown to synthesize further TGF-β[35]. TGF-β stimulates the production of extracellular matrix protein and collagen by fibroblasts *in vitro*[36]. *In vitro* it decreases collagenase production by cultured fibroblasts and increased production of a metalloproteinase collagenase inhibitor[37]. Injected *in vivo*, TGF-β induces reversible fibroplasia[38]. It is thus implicated as a critical peptide controlling collagen and matrix deposition In a collagen suspension applied at a time of wounding it accelerates the gain in strength of both linear rat skin incisions[4] and healing rabbit linear stomach wounds[6] and reverses the deleterious effects of steroid therapy[7] on skin wound breaking strength. A local application of TGF-β in a collagen suspension partially reversed the deleterious effects of steroid therapy on breaking load in healing ileal wounds; a similar though non-significant trend was seen with colonic wounds.

The pharmacological manipulation of healing with topically applied growth factors offers promise[39] Intestinal wound failure has serious implications and is more likely to occur when the processes of repair are impaired. The use of topical wound healing agents in gastrointestinal surgery, particularly in situations of impaired healing, may present therapeutic advantages

## Acknowledgements

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# Factors influencing the healing of distal amputations performed for lower limb ischaemia

*A total of 235 toes were amputated during 125 operations on 100 consecutive patients with lower limb ischaemia. The overall amputation wound healing rate for the series was 58·4 per cent and limb salvage was achieved in 66 patients. Toe amputation was performed under local anaesthesia in 57 cases and 32 (56 per cent) of these healed primarily, not significantly different from the healing rate of 41 (60 per cent) of 68 under general anaesthesia. Reconstructive arterial surgery was performed in conjunction with toe amputation in 39 patients; the healing rate with reconstruction was 32 (82 per cent) of 39, significantly better than the 41 (48 per cent) of 86 patients not undergoing bypass surgery (P < 0·001). There was no difference in healing rates when comparing diabetic and non-diabetic patients. Multiple regression analysis demonstrated that reconstructive arterial surgery was the only factor which had an independent and significant influence on toe amputation healing. The use of local anaesthesia for distal amputation has no deleterious effects on wound healing.*

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Distal amputation leads to improved rehabilitation but exposes the patient to an increased risk of failure of wound healing, which varies between 17 and 69 per cent[1–8]. The key to this problem lies in selecting patients in whom a distal amputation will heal, an array of both invasive and non-invasive methods of predicting outcome having been described[2–4,9–12]. The aim of this retrospective study was to provide further insight into the nature of success or failure of distal amputation in patients with lower limb ischaemia, with particular emphasis on the role of reconstructive arterial surgery. The setting was a large district general hospital where toe amputation has often been carried out under local anaesthesia. The influence of the method of anaesthesia was made a focal point of the study.

## Patients and methods

The records of 100 consecutive patients who underwent toe amputation for distal ischaemia were reviewed retrospectively. Toe amputation was defined as removal of one or more toes either distal to or at the level of the metatarsal neck. More proximal amputations were excluded from this study. Individual operations were considered as single amputation procedures, irrespective of the number of toes amputated. Arteriography was performed according to clinical indications, and decisions about the suitability of patients for bypass grafting and toe amputation were made on clinical and angiographic grounds. The type of anaesthesia used (general anaesthesia or local anaesthetic block) was dependent on the fitness of individual patients and the personal preference of the surgeon. Outcome was assessed on the basis of wound healing and the need for further amputation. The influence of several factors on outcome was recorded. number and position of amputated toes, diabetic status, present and past smoking habits, concomitant reconstructive arterial surgery, concomitant angioplasty, state of the leg pulses, evidence of infection in association with ischaemia, ankle:brachial pressure index (ABPI) at the time of surgery, haemoglobin, blood urea, serum albumin, grade of operating surgeon, type of anaesthesia, level of amputation, method of wound closure, subjective assessment of wound edge bleeding at operation. Statistical analysis was performed using the Mann–Whitney *U* test for continuous variables and the $\chi^2$ test for discrete variables. Multivariate Cox regression analysis[13] was used to quantify the observed relationship between each of the 17 factors studied and the risk of failure of healing in toe amputations. This statistical method uses stepwise regression analysis to identify those variables that independently and significantly influence outcome.

### *Technique of local anaesthetic nerve blocks*

The five nerves supplying the foot (tibial, sural, saphenous, superficial peroneal and deep peroneal) and individual digital nerves can be blocked with relative ease[14,15]. Local blocks provide effective anaesthesia for distal amputations because the nerves concerned not only supply the relevant skin but also provide muscular and articular branches to the surrounding tissues.

Tibial and sural nerve blocks were performed with the patient lying prone. The tibial nerve was blocked by infiltration of 8–12 ml local anaesthetic between the Achilles tendon and the upper border of the medial malleolus. The sural nerve was blocked by subcutaneous infiltration (5–8 ml) between the Achilles tendon and the lateral malleolus.

For superficial peroneal, deep peroneal and saphenous nerve blocks the patient lay supine. The superficial peroneal nerve was blocked by raising a subcutaneous weal (5–10 ml) half way between the anterior border of the tibia and the lateral malleolus at the level of the talocrural joint. The deep peroneal nerve was blocked at the level of the ankle by a 5–10 ml infiltration placed just lateral to the anterior tibial artery, or between the tendons of extensor hallucis longus and tibialis anterior if no pulse was present. The saphenous nerve was blocked by infiltration around the long saphenous vein in relation to the medial malleolus, in order to avoid intravenous injection it is important to aspirate before injecting 5–10 ml anaesthetic solution.

Digital nerves were blocked either in the intermetatarsal spaces or the web spaces associated with each toe. The former allowed ray amputation through the neck of the metatarsal and the latter was suitable for toe amputation. Skin weals were raised on the dorsum of the foot over the proximal end of the metatarsal spaces either side of the toe to be blocked; 2–3 ml local anaesthetic was infiltrated fanwise to include the plantar aspect of the metatarsal bone without piercing the sole of the foot.

The anaesthetic used was usually 0·5–1·0 per cent lignocaine, but other local anaesthetics such as prilocaine and bupivacaine were acceptable substitutes. Local anaesthetic solutions containing adrenaline were avoided. The blocks took 10–30 min to act and generally lasted for up to 2 h. Digital nerve blocks were used for both ray and distal amputation of single toes, for multiple toe amputation the relevant nerves to the foot were blocked at the level of the ankle. A complete block of all five nerves was avoided, a combination of three nerve blocks being the most usual requirement. Most nerve blocks in this series were performed by the operating surgeon.

## Results

A total of 235 toes were amputated in 125 operations performed on 100 patients (66 men, 34 women; mean age 67 (range

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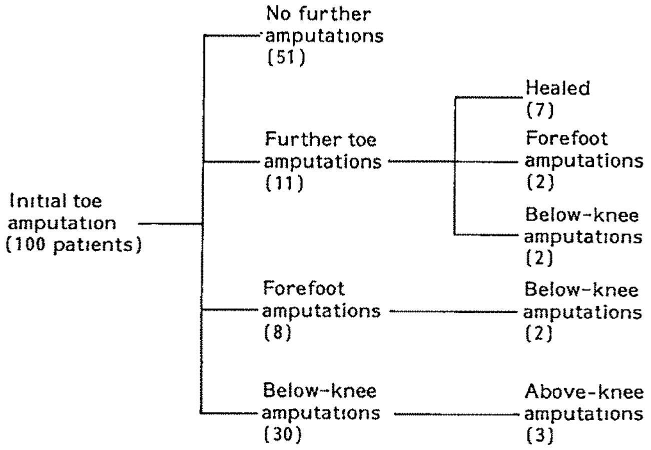
Initial toe amputation (100 patients)
No further amputations (51)
Further toe amputations (11)
Healed (7)
Forefoot amputations (2)
Below-knee amputations (2)
Forefoot amputations (8)
Below-knee amputations (2)
Below-knee amputations (30)
Above-knee amputations (3)

**Figure 1** *Outcome after toe amputation*

41–94) years). Seventy-seven patients were smokers or former smokers of cigarettes and 55 were diabetic.

No further amputation surgery was needed for 51 of the patients (*Figure 1*); 11 patients underwent a further toe amputation procedure, seven of which were successful. In the four patients in whom this second amputation failed, two forefoot and two below-knee amputations were required. Eight patients with failed toe amputations underwent a forefoot amputation as a revisional procedure; two of these failed and resulted in below-knee amputation. The remaining 30 patients with failed toe amputation proceeded directly to below-knee amputation, and three of these had to be revised to above-knee amputation. Limb salvage was therefore achieved in 66 of the 100 patients undergoing an initial toe amputation.

The overall amputation wound healing rate for the series was 58·4 per cent. Of the 68 amputations in diabetic patients, 36 (53 per cent) healed successfully. Although this was lower than the healing rate in non-diabetic patients (37 of 57; 65 per cent), the difference was not statistically significant.

General anaesthesia was used for 68 toe amputations and the remaining 57 were performed under a combination of local anaesthetic blocks. All operations performed under local anaesthetic block were completed successfully without recourse to other methods of anaesthesia. Distal amputations performed under local anaesthesia healed in 32 of 57 cases (56 per cent), not significantly different from the healing rate of 41 of 68 (60 per cent) for cases performed under general anaesthesia.

Reconstructive arterial surgery was performed on 39 patients either 1–2 weeks before, or at the same time as, toe amputation. Nine of these operations were reconstructions for disease proximal to the inguinal ligament (one aortoiliac, six aortofemoral and two axillofemoral bypass grafts) and 30 were distal bypass operations (23 femoropopliteal and seven femorodistal grafts). The 3-month graft patency rates for proximal reconstructions, femoropopliteal and femorodistal grafts were 100, 74 and 57 per cent respectively. In the 30 patients with a patent graft at 3 months the toe amputation healing rate was 93 per cent; if the unsuccessful grafts are added to this the toe amputation healing rate in the reconstructive surgery group overall was 82 per cent. In contrast, only 41 of 86 amputations (48 per cent) performed in patients not undergoing bypass surgery healed successfully ($\chi^2 = 13{\cdot}05$, $P < 0{\cdot}001$).

The influence of diabetic status and reconstructive surgery on healing rates is shown in *Figure 2*. Of 16 non-diabetic patients undergoing distal reconstructive surgery, amputation wounds failed to heal in three, and in two of these the graft had occluded within the first month. In the diabetic group three of 14 distal grafts occluded within the first month and toe amputations failed in all three.

The mean ABPI for the entire group was 0·68 (range 0·19–1·36). There was no statistically significant difference between the ABPI in patients whose amputations healed (mean 0·73, range 0·39–1·36) and that in patients whose amputations did not heal (mean 0·62, range 0·19–1·10). However, the ABPI in the group after bypass operation (mean 0·87, range 0·54–1·32) was significantly higher ($P < 0{\cdot}01$, Mann–Whitney *U* test) than that in the group which had not undergone bypass (mean 0·55, range 0·19–1·36). Multivariate regression analysis demonstrated that concomitant reconstructive arterial surgery was the only factor which had an independent and significant effect on healing (standardized regression coefficient 3·06; $P = 0{\cdot}002$), confirming the findings of the single variable analysis.

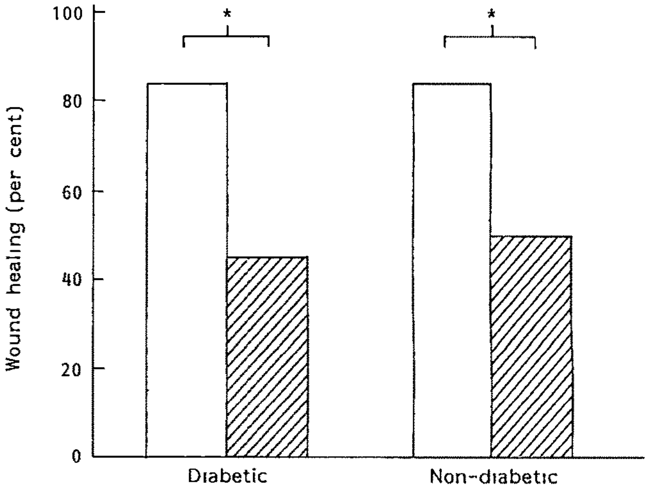

**Figure 2** *Influence of reconstructive surgery and diabetic status on amputation wound healing.* □, *Surgery,* ▨, *no surgery* *$P < 0{\cdot}001$ (*Mann–Whitney* U *test*)

## Discussion

The rationale for a conservative approach to distal gangrene is straightforward: the salvage of enough useful foot will allow rehabilitation without use of a prosthesis. The major problem with distal amputation is that it has been associated with a high rate of failure and reamputation. Careful patient selection is needed.

Doppler ultrasonographic measurement of ankle artery pressure has been the simplest and most widely employed method of attempting to predict outcome after amputation, but there has been considerable disagreement over the minimum pressure required for healing (quoted figures[1,7] ranging from 35 mmHg to 60 mmHg). Present data suggest that while an unfavourable pressure is sometimes compatible with successful healing in both diabetic and non-diabetic patients, a good pressure is no guarantee of success. The decision to perform distal amputation therefore cannot be made solely on the basis of non-invasive pressure measurements.

The results of the present study suggest that local anaesthesia has no deleterious effects on wound healing. Most of the amputations were performed on a group of relatively unfit patients, often with ischaemic heart disease, hypertension and diabetes. Avoidance of general anaesthesia in such a group is advantageous and we feel that toe amputation under local anaesthetic has a useful role in this situation.

The only factor affecting healing in this series was the use of concomitant reconstructive vascular surgery. Patients who were suitable for revascularization surgery fared a great deal better than those who were not. The healing rate of amputations performed on patients with arterial lesions deemed to be unreconstructable was only 48 per cent, at least half of this group would benefit from a more proximal amputation as a first procedure. Unfortunately there are still no clear predictors of success for such patients, for whom more sophisticated investigations[10,11] may be of benefit. We continue to manage these cases on clinical criteria alone and feel that local anaesthetic blockade is useful in this setting because it renders toe amputation a more minor undertaking.

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# Announcement

## Eurosurgery 1992

The 2nd European Congress of Surgery under the auspices of Eurosurgery will take place in Brussels in June 1992. This meeting will pursue the aims of Eurosurgery to promote research and training in surgery.

There will be national sessions sponsored by the Associations of Surgery of all participating nations Areas of topical interest will be covered in symposia and free paper sessions in areas of general interest and in the specialist fields of abdominal, thoracic, transplantation, trauma, paediatric, endocrine, plastic and vascular surgery. There will be several symposia related to surgical training.

The abstracts of the free paper communications will be published in a special supplement of *The British Journal of Surgery*

Further details and registration forms may be obtained from the Congress of Secretariat Eurosurgery 1992, Brussels International Trade Fair, Place de Belgique, B1020 Brussels, Belgium. Telephone: 322 477 0457. Facsimile · 322 477 0391.

**Br. J. Surg. 1992, Vol. 79, January, 76–78**

# Early reoperation after major vascular surgery: a four-year prospective analysis

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*Between 1 January 1985 and 31 December 1988, 1176 major vascular operations were performed on 1040 patients by the Oxford Regional Vascular Service, of which 136 (12 per cent) were reoperations within 30 days of the initial procedure (110 patients). Sixty-seven (49 per cent) of the reoperations were attempted revascularizations, 43 (32 per cent) were amputations, and surgery for bleeding accounted for 18 (13 per cent). Of the first reoperations 71 (65 per cent) were successful, but among the remaining 39 patients, 17 underwent 26 further reoperations, 15 of which were reoperations for revascularization. The 30-day mortality rate for patients undergoing one reoperation was 13 per cent; this rose to 35 per cent if more than one reoperation was performed. Early reoperation after major vascular surgery is common and carries a high operative mortality. This should be borne in mind when obtaining the informed consent of the patient.*

In the last decade there has been an increase in the number and difficulty of vascular operations performed[1–3]. Most patients are elderly and vascular surgery carries a substantial morbidity and mortality[4] A relatively neglected aspect of surgical audit is the incidence and outcome of early reoperations to deal with surgical complications or because the first operation fails to achieve the intended result Early reoperation rates reported from vascular surgical practice range from 4 to 20 per cent[4–6], but this figure is likely to depend on the nature and effectiveness of the practice This study audits the nature and outcome of all reoperations performed within 30 days of a major vascular operation.

## Patients and methods

Data were obtained from the prospectively collected weekly audit of the Oxford Regional Vascular Service All reoperations undertaken within 30 days of major vascular surgery performed between 1 January 1985 and 31 December 1988 were reviewed The indication for reoperation was recorded as · (1) revascularization; (2) amputation or revision of previous amputation level, (3) bleeding; or (4) other The outcome of the procedure was noted

## Results

In the 4-year study period, 1040 patients had a major vascular operation and 110 (10·6 per cent) underwent 136 reoperations within 30 days. There were 79 men and 31 women with a median age (range) of 67 (12–93) years. One reoperation was required for 93 (8·9 per cent) patients, 11 (1·1 per cent) required two, and six (0 6 per cent) patients underwent three to five reoperations.

*Table 1* shows the relationship between the type of surgery and reoperation rates. Aortic surgery was performed in 263 patients, 143 (54 per cent) of whom had a tube graft and 120 (46 per cent) a bifurcated graft. All 143 tube grafts were inserted in patients with an abdominal aortic aneurysm, and of these 71 were emergencies with a reoperation rate of 15 per cent; 72 were elective, with a reoperation rate of 3 per cent. Of the 120 patients who had a bifurcated graft inserted, 66 were for aneurysmal disease and 54 for occlusive disease with reoperation rates of 9 per cent and 15 per cent respectively. All carotid endarterectomies were elective.

The indications for the first and subsequent reoperations are shown in *Tables 2* and *3* respectively. Of the reoperations 67 (49 per cent) were attempted revascularizations, 43 (32 per cent) amputation and 18 (13 per cent) for bleeding. Reamputation at a higher level accounted for 20 operations With respect to aortic surgery, nine patients had a reoperation for bleeding; four died, two from exsanguination. The outcome of the first reoperation related to its objective is shown in *Table 4*

The following categories required reoperation in the 'miscellaneous' group: axillobifemoral bypass (four), thrombectomy of a previous synthetic graft (three), axilloaxillary artery bypass (two), profundoplasty (two), femoral aneurysm (two), false femoral aneurysm (two), superficial femoral artery repair after trauma (one), superficial femoral artery endarterectomy (one). refashioning of an aortobifemoral graft (one), superior mesenteric artery thrombectomy (one) and fasciotomy (one).

Of the 110 patients undergoing reoperation, 18 (16 per cent) died within 30 days of the primary operation (*Table 5*). The mortality rate after one reoperation was 13 per cent; this rose to 35 per cent in the 17 patients who had more than one reoperation Eight (30 per cent) of the 27 patients undergoing reoperation after aortic surgery died, six of these deaths occurring after emergency aneurysm surgery One patient died after reoperation following a femoropopliteal bypass. The causes of death in the 18 patients were cardiac (eight), respiratory (three), renal (two), cerebrovascular accidents (two), exsanguination (two) and upper gastrointestinal haemorrhage (one).

**Table 1** *Patients undergoing reoperation after primary surgery*

| Operation | No of primary operations | No of patients undergoing reoperation |
|---|---|---|
| Aortic surgery | 263 | 27 (10) |
| Amputation | 216 | 22 (10) |
| Embolectomy | 152 | 19 (13) |
| Femoropopliteal bypass | 138 | 14 (10) |
| Carotid endarterectomy | 60 | 4 (7) |
| Femorofemoral crossover | 46 | 4 (9) |
| Miscellaneous | 165 | 20 (12) |

Values in parentheses are percentages

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*Paper presented at the meeting of the Association of Surgeons of Great Britain and Ireland held in Oxford, UK on 3–5 April 1991*

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**Table 2** *Indications for first reoperation*

| | | Aim of reoperation | | | |
|---|---|---|---|---|---|
| Primary operation | No. first reoperations | Revascularization | Amputation | To arrest bleeding | Other |
| Aortic surgery | 27 | 14 | 2 | 9 | 2 |
| Amputation | 22 | – | 18 | 1 | 3 |
| Embolectomy | 19 | 12 | 5 | 1 | 1 |
| Femoropopliteal bypass | 14 | 9 | 3 | 2 | – |
| Carotid endarterectomy | 4 | 3 | – | 1 | – |
| Femorofemoral crossover | 4 | 2 | – | 2 | – |
| Miscellaneous | 20 | 12 | 6 | 1 | 1 |
| Total | 110 | 52 | 34 | 17 | 7 |

**Table 3** *Indications for second and subsequent reoperations*

| | | | Aim of reoperation | | | |
|---|---|---|---|---|---|---|
| First operation | No. of patients | No of operations | Revascularization | Amputation | To arrest bleeding | Other |
| Aortic surgery | 6 | 7 | 5 | 1 | – | 1 |
| Amputation | 1 | 2 | – | 2 | – | – |
| Embolectomy | 3 | 3 | 2 | 1 | – | – |
| Femoropopliteal bypass | 6 | 10 | 5 | 4 | 1 | – |
| Carotid endarterectomy | 0 | – | – | – | – | – |
| Femorofemoral crossover | 0 | – | – | – | – | – |
| Miscellaneous | 1 | 4 | 3 | 1 | – | – |
| Total | 17 | 26 | 15 | 9 | 1 | 1 |

**Table 4** *Outcome of first reoperation in relation to its objective*

| | | Outcome | |
|---|---|---|---|
| Objective | *n* | Success | Death |
| Revascularization | 52 | 33 | 9 |
| Arrest bleeding | 17 | 12 | 4 |
| Obtain healing | 34 | 24 | 4 |
| Other | 7 | 2 | 1 |
| Total | 110 | 71 | 18 |

Outcome numbers exclude failed operations that did not result in death

**Table 5** *Mortality of reoperation related to primary procedure*

| Primary operation | No of patients undergoing reoperation | No. of deaths* |
|---|---|---|
| Aortic surgery | 27 | 8 |
| Amputation | 22 | 4 |
| Embolectomy | 19 | 4 |
| Femoropopliteal bypass | 14 | 1 |
| Carotid endarterectomy | 4 | 0 |
| Femorofemoral crossover | 4 | 0 |
| Miscellaneous | 20 | 1 |
| Total | 110 | 18 |

*Within 30 days of primary operation

**Table 6** *Percentage of patients undergoing reoperation in three different centres*

| | Centre | | |
|---|---|---|---|
| | Cleveland (1979)[5] | Sweden (1989)[6] | Oxford (1990) |
| No of operations | 8824 | 1569 | 1176 |
| Type of operation | | | |
| Aortic surgery | 6·8 | 9·2 | 10 |
| Femoropopliteal bypass | 15·3 | n.g. | 12 |
| Embolectomy | 19·6 | 21·8 | 13 |
| Amputation | 8·4 | n.g. | 10 |
| Carotid | – | 3·5 | 7 |
| All | 8·4 | 11 | 12 |

n.g., Data not given

## Discussion

Clinical audit of vascular surgical practice is commonplace[5–7]: it is an essential part of local quality control, but information is usually neither original nor of much general interest. Reoperation rates are thought to be high in vascular surgery but have been little studied.

The overall early reoperation rate in this study was 11·6 per cent and a comparison with results from Cleveland[5] and Sweden[6] reveals similarities (*Table 6*). There has been no marked change in the rate of early reoperation. Vascular surgical results may be better than they were a decade ago but some patients who would not then have been considered suitable for operation now undergo surgical treatment[4]

There is little information on the reoperation rate and outcome in aortic surgery[8–11]. In the nine patients in this study requiring reoperation for haemorrhage there was a 44 per cent mortality rate, emphasising the dire consequences of failure to secure adequate haemostasis in situations where tissue tamponade will not limit blood loss. The high reoperation rate (15 per cent) following elective aortic surgery for occlusive disease contrasts with that for elective aortic aneurysm surgery (3 per cent) when tube grafts were used: the surgical treatment of aortic occlusive disease is usually more difficult than the same operation performed for aneurysmal disease.

Reoperation rates following femoropopliteal bypass, amputation and embolectomy are similar to those reported in other series[5,6,12–17]. Mortality rates were three times higher for reoperations after amputation and embolectomy than after femoropopliteal bypass and probably reflect a poorer preoperative condition.

The only primary procedure which was always performed electively was carotid endarterectomy and this was associated with a low reoperation rate and no mortality. Suspected thrombosis was the indication for reoperation in three (5 per cent) patients in two of whom occlusion had occurred. Other series have reported an incidence of acute thrombosis following carotid surgery of 2–5 per cent[18,19].

Two-thirds of reoperations in this series achieved a successful outcome at the time of discharge from hospital. Operative mortality was greatest in patients undergoing reoperation after emergency aortic surgery and was three times greater after multiple reoperations than after a single reoperation. The causes of death recorded on death certificates were similar to those reported in other audits[20,21] and CEPOD (Confidential Enquiry into Perioperative Deaths) data[22]. The data on surgery for aortic aneurysm showed that reoperation is five times more likely after emergency than after elective surgery. Reoperation rates in vascular surgery are similar to those in other branches of surgery where operations of comparable magnitude are undertaken. In colorectal surgery restorative proctocolectomy is associated with reoperation rates of 18–36 per cent[23,24].

This study raises an issue of informed consent[25] Patients are advised that damage to the recurrent laryngeal nerve may occur during thyroidectomy and that recanalization of the vas may occur after vasectomy[26,27]: the risk of the former is about 1 per cent and the latter less than 0·1 per cent. The reoperation rate in this study for patients undergoing vascular surgery is more than 10 per cent and carries an overall mortality rate of 16 per cent. This analysis suggests that it is advisable to inform patients of the incidence and risk of reoperation.

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# Doppler ultrasonographic localization of the cephalic vein: a new technique to simplify the insertion of central venous catheters

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The cephalic vein provides a safe route for insertion of a central venous catheter under local anaesthesia, but difficulty may be encountered with the anatomical localization of the vein, particularly in obese patients. This study assessed the ability of an ultrasonographic Doppler probe to localize the cephalic vein before operation.

## Technique

All patients referred for insertion of a Hickman central venous catheter were entered into the study provided they gave informed consent The surgeon estimated where he thought the course of the cephalic vein was in the region between the shoulder joint and the clavicle, and this was marked with a pen line over 2–3 cm. An assistant positioned a 5 MHz portable pulsed Doppler ultrasonographic probe over the same region while the surgeon stroked the cephalic vein in the upper arm in a cephalad direction (*Figure 1*). The probe was moved until a clear signal from the cephalic vein was registered when the cephalic vein was stroked. The point of maximum signal intensity was noted

To confirm that identification of the cephalic vein had been achieved, the surgeon interrupted the signal by applying pressure to the patient's upper arm in the course of the cephalic vein between his stroking hand and the probe (*Figure 2*) Abolition of the signal confirmed that the cephalic vein had been located The course of the ultrasonically identified cephalic vein was marked by a 2–3-cm line.

The procedure was repeated on the contralateral side The surgeon then made a decision as to which side had the greater signal intensity and this side was explored if there was no contraindication. If the signals were comparable in intensity, the right side was usually explored.

Under local anaesthesia a vertical incision was made across the midpoint of the ultrasonically derived line marking. Once the cephalic vein had been located, its surface marking was marked with a pen This was determined as the shortest distance from the skin to the vein. To minimize the potential movement of the reference points after incision and separation of the wound edges, the skin retractors were removed and the wound edges reopposed without tension (to reconstitute the skin markings) before the distances from the surface marking of the cephalic vein to the ultrasonically localized site (the 'Doppler distance') and the surgeon's site (the 'surgeon distance') were finally measured. The Hickman catheter was then inserted into the vein via a subcutaneous tunnel and the position of the line was verified with fluoroscopy

## Results

Ten men and seven women were entered into the study. The median age was 71 (range 24–85) years. The indications for inserting a Hickman catheter were: total parenteral nutrition (12), chemotherapy for leukaemia (four) and long-term administration of antibiotics (one).

Sixteen catheters were successfully introduced. The one failure was in a patient receiving long-term antibiotics for infection of the hip joint. Both of this patient's cephalic veins were successfully localized, but they were too small to catheterize

The median surgeon distance from the cephalic vein was 2·0 (range 0–4) cm. The median Doppler distance from the cephalic vein was 0 (range 0–1·5) cm. The distances and the direction (above or below) in which the surgeon and ultrasonography erred are shown in *Figure 3*; the latter was significantly better ($P < 0.01$, Mann–Whitney $U$ test).

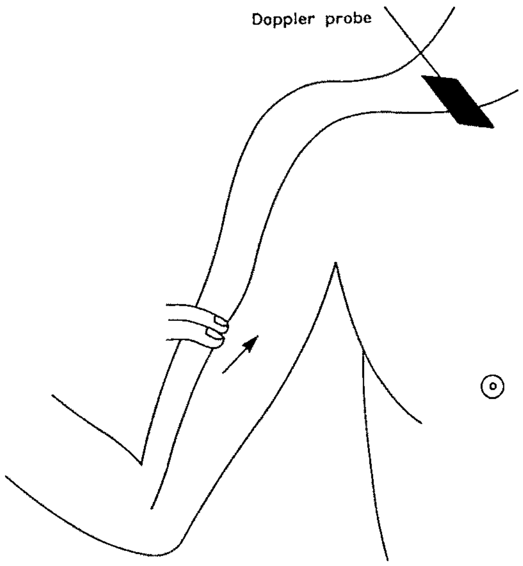

**Figure 1** *As the cephalic vein is stroked in the upper arm, the Doppler ultrasonographic probe is manoeuvred to the point of maximal signal intensity*

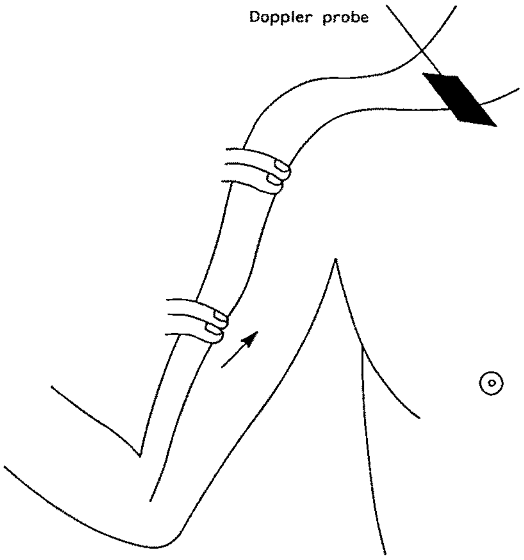

**Figure 2** *To confirm that the cephalic vein has been localized, pressure is applied in the course of the cephalic vein between the stroking hand and the Doppler ultrasonographic probe; the signal disappears*

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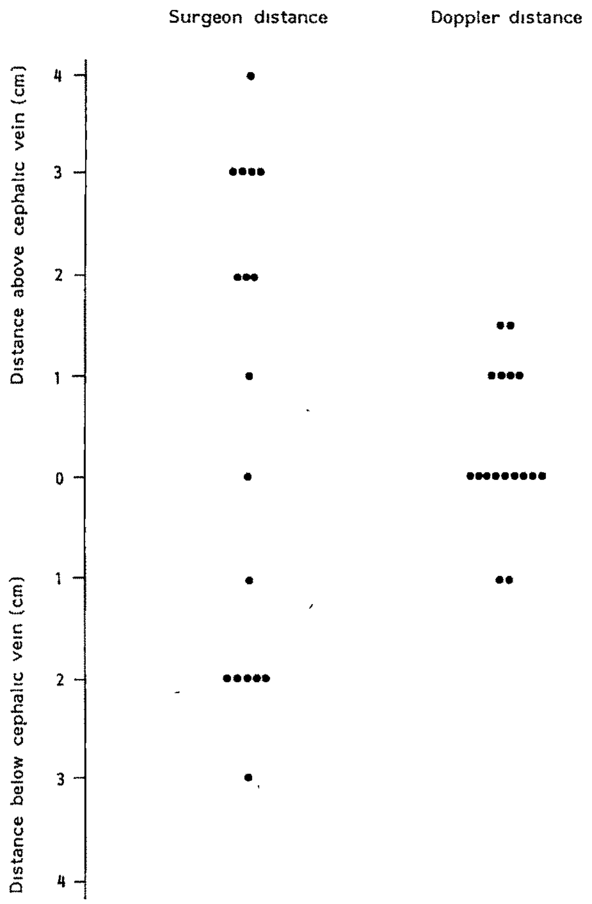

**Figure 3** *Distance from the cephalic vein to the points where the surgeon (surgeon distance) and Doppler ultrasonographic probe (Doppler distance) estimated the cephalic vein to lie. Each dot represents one measurement.* $P < 0{\cdot}01$ (*Mann–Whitney* U *test*)

## Discussion

Central venous cannulae may be inserted using either a percutaneous puncture technique or an open surgical approach. There are a number of veins to choose from, including the subclavian, internal jugular, external jugular and cephalic veins. Neck lines are generally less well tolerated as they are uncomfortable. The percutaneous route to the subclavian vein is popular, but the complications that arise from this blind approach include pneumothorax (0–6 per cent)[1,2], bleeding secondary to laceration of the subclavian artery (4–7 per cent)[1,3], and occasionally haemothorax, hydrothorax and nerve injury[4,5].

For these reasons, the use of the open or cut-down approach, which is safer but more time-consuming, has been advocated[5,6], particularly when the patient has a bleeding diathesis secondary to disease[6]. The approach to the cephalic vein is via an incision across the most lateral portion of the deltopectoral groove, where the vein is more superficial. Within the groove lies a constant strip of fat which is a reliable landmark for the vein itself. However, it can prove difficult to identify the deltopectoral groove, particularly in obese patients; the vein may be of variable size (it is generally smaller in women[7]) and may be thrombosed owing to previous peripheral vein catheterization in the forearm. These difficulties explain in part why this cut-down approach often takes longer than the percutaneous method.

This study illustrates how inaccurate surgeons can be in estimating where the cephalic vein lies. Using a Doppler ultrasonographic probe, readily available in most surgical departments, we have developed a simple technique for localizing the cephalic vein with greater accuracy. Localization of the cephalic vein with the probe before operation has three advantages. It enables the surgeon to compare the relative intensity of the signals between the right and left cephalic veins, and thus gives an indication of which side may be better explored first. The incision may more accurately be placed over the site of the vein; this is especially helpful when the operation is performed using local anaesthesia. It gives the surgeon greater confidence to continue to search for the vein in a particular area when it is not easy to identify.

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# Laser-assisted angioplasty for arterial occlusion of the lower limb: initial results and follow-up

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*A flashlamp-pumped pulsed dye laser operating at either 480 or 504 nm, coupled to an integral ball-tipped optical fibre, was used to recanalize occluded lower limb arteries. All channels created by the laser were augmented with balloon dilatation. We have treated 78 limbs in 71 patients; 46 limbs (59 per cent) had rest pain and 22 (48 per cent) of these had tissue loss. The median occlusion length was 18 (range 0·5–58) cm. Technical success was achieved in 58 limbs (74 per cent) with clinical success in 46 (59 per cent). Success rates fell with increasing length of occlusion. Two patients died in the perioperative period. A subgroup of 22 patients with marked discrete arterial calcification had a lower technical success rate than the subgroup without calcification (50 per cent* versus *84 per cent,* $P < 0{\cdot}01$*). Both subgroups displayed a similar pattern of reclosure during follow-up. The cumulative patency rate after technical success was 67 per cent at 6 months and 45 per cent at 12 months. Forty-six (59 per cent) limbs avoided bypass surgery or amputation. Laser-assisted angioplasty may offer an alternative to femoropopliteal bypass, although the former procedure is not as durable.*

Less invasive treatment of arterial occlusive disease began with the description of transluminal angioplasty by Dotter and Judkins in 1964[1]. Its widespread application followed the introduction of balloon catheters by Grüntzig and Hopff in 1974[2]. At present, percutaneous transluminal angioplasty is used to treat patients with stenotic or short segment occlusive disease. However, even in the most skilful hands, failure becomes more likely as the length of the occlusion increases[3–6].

The development of lasers and their ability to ablate biological tissues led to reports of recanalization of human arteries[7,8]. These early procedures were performed with bare optical fibres, whose traumatic ends readily gave rise to perforation. The use of metal caps[9,10] and the attachment of rounded sapphire probes to the end of fibres[11] reduced the problem of perforation[12–15] and allowed the development of clinical programmes using continuous-wave lasers. The mechanism of recanalization with these devices was thermal ablation of plaque[16,17], with the potential for thermal injury to adjacent normal arterial wall

More recently, it has been demonstrated that pulsed laser energy is capable of ablating vascular tissue without thermal injury if the pulses are of sufficiently short duration and their rate does not exceed the thermal relaxation time of the tissue[18].

Pulsed dye lasers operating in the blue-green range of the visible spectrum have been shown *in vitro* to ablate preferentially human atherosclerotic plaque[19–21] and calcified plaque[22], compared with normal arterial wall. Preferential ablation is due to the presence of yellow chromophores within lipid-rich plaques[23] and the generation of laser plasmas at the surface of calcified plaque[22]. These lasers are capable of recanalizing occluded peripheral arteries in humans[24] using modified optical fibres, which comprise ball-tips in molecular continuity with the fibre These devices are able to transmit short pulses with high peak powers without disintegrating.

A clinical series of 78 limbs treated over a period of 37 months from Feburary 1988 until March 1991 is described.

## Patients and methods

Patients presenting to the vascular surgical unit of St Bartholomew's Hospital, London, were assessed for suitability for laser-assisted angioplasty if they had evidence of arterial occlusion of their superficial femoral artery, popliteal artery or run-off vessels and were not considered suitable for percutaneous transluminal angioplasty. When the study began the hospital ethical committee stipulated that the patients must be at the point of amputation or facing a graft with a high likelihood of failure. All patients in ths study gave fully informed consent before laser-assisted angioplasty. As the study progressed the terms of suitability were broadened to include patients with severe claudication in whom it would be desirable to avoid grafting, but in the majority of whom transluminal angioplasty was likely to fail due either to the occlusion being longer than 10 cm ($n = 46$), or occlusion of the artery at the origin of the superficial femoral artery ($n = 23$) The results of this series cannot therefore be readily measured against those of percutaneous transluminal angioplasty.

All patients had evidence of critical limb ischaemia[25] or severe disabling claudication. There were 44 men and 27 women of median age 73 (range 40–87) years, 16 (23 per cent) patients were diabetic, 19 (27 per cent) patients had had a myocardial infarction or had disabling angina, and eight (11 per cent) patients had had a stroke or transient ischaemic attack. Of the 78 affected limbs, 46 (59 per cent) had rest pain, with ulceration or gangrene in 22 (28 per cent); the remainder had severe disabling claudication.

Before angioplasty all patients underwent arteriography, ankle brachial Doppler ultrasonography testing at rest and after exercise (when able to exercise) and duplex scanning of the involved limb. Duplex ultrasonography was used to confirm total vessel occlusion and to characterize the nature of the occluding lesion (*Figure 1*). Particular attention was paid to the presence or absence of arterial wall calcification, a factor known to affect the outcome of angioplasty (*Figure 2*)

Preoperative angiography demonstrated total occlusion of segments of the lower limb vascular tree (*Table 1*), with a median occlusion length of 18 (range 0·5–58) cm Mean(s.d ) preoperative ankle: brachial pressure index (ABPI) at rest was 0·52(0 19) A number of limbs had a high preoperative ABPI despite evidence of critical ischaemia, indicating that their arteries were incompressible. This finding was frequently associated with arterial calcification.

All but four patients were treated under general or epidural anaesthesia Sixty-nine limbs were treated through a cut-down incision, sited in the groin in 66 cases. In the remaining three cases, occlusion in the distal circulation was approached in a retrograde manner via an incision sited downstream. The reasons for using an open approach varied during the study. The first 25 cases were treated using a cut-down procedure to optimize entry of the device into the artery while the technique was being learned Of the remaining 53 limbs, 23 had

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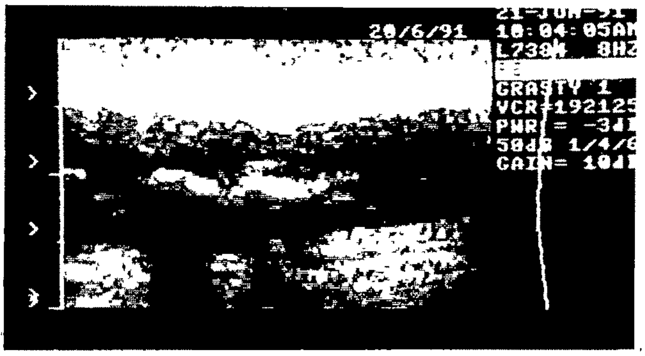

**Figure 1** *Duplex scan of an occluded femoral artery showing heavily calcified plaque protruding into the vessel lumen and casting a strong acoustic shadow*

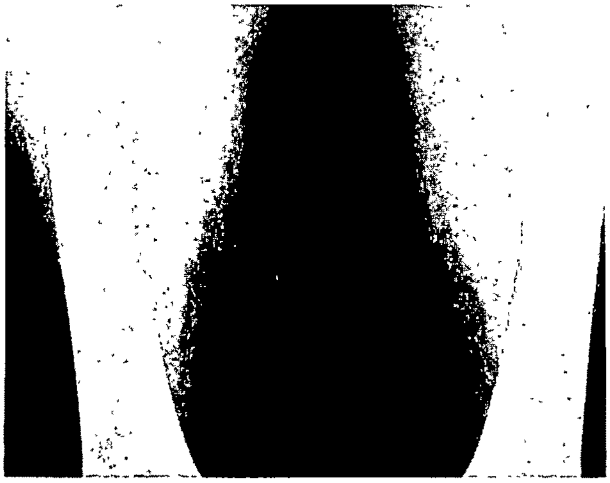

**Figure 2** *Plain radiograph of both thighs in a male patient showing marked calcification of both superficial femoral arteries*

**Table 1** *Outcome of laser-assisted angioplasty by length of lesion*

| Lesion length (cm) | Number | Technical success | Clinical success |
|---|---|---|---|
| <3 | 2 (3) | 2 (100) | 2 (100) |
| 3–7 | 11 (14) | 10 (91) | 10 (91) |
| >7 and <10 | 9 (12) | 5 (56) | 1 (11) |
| 10–20 | 19 (24) | 14 (74) | 14 (74) |
| >20 | 37 (47) | 27 (73) | 19 (51) |
| Total | 78 | 58 (74) | 46 (59) |

Values in parentheses are percentages

occlusion of the origin of the superficial femoral artery, precluding a percutaneous approach by direct femoral puncture. Nine limbs required surgery to improve the arterial inflow at the same time as laser-assisted angioplasty A further 13 limbs had an attempted percutaneous procedure, which was successful in nine. This reflects the learning curve of the operators

The laser delivery device used was a quartz optical fibre (Polymicro Technologies, Phoenix, Arizona, USA), 600 $\mu$m in diameter, on which an integral ball-tip (Dunn Laboratories, St. Bartholomew's Hospital, London, UK) was fashioned. The fibre was backloaded into a standard balloon angioplasty catheter to create a combined laser and balloon dilatation device (*Figure 3*). This avoided the need to cross the lesion with a laser fibre and then recross it with a guidewire before balloon dilatation, a situation that could result in guidewire dissection No attempt was made to cross the lesion with a guidewire first, as reported in some studies, as we believed that guidewire dissection would prejudice the results of lasing.

The outcome of the procedure was classified as a technical success when there was successful crossing of the lesion and balloon dilatation with a satisfactory angiographic appearance at the end of the procedure A clinical success was recorded when there was abolition of rest pain, demarcation of gangrene, or ulcer healing, or improvement in claudication with a rise in the ABPI of $\geqslant 0{\cdot}15$ Where obvious clinical benefit was obtained without significant change in the ABPI, for example the abolition of rest pain, this overrode the ABPI requirement. This occurred in three cases

Following measurement of the power output, the device was introduced into the artery and advanced to the point of occlusion At this time the laser (Candela MDL-1P; Candela Laser Corporation, Wayland, Massachusetts, USA) was activated. We used wavelengths of 480 or 504 nm, generated by flashlamp pumping of coumarin dyes dissolved in an ethylene glycol:water mixture. The laser was pulsed at 10 Hz, generating pulses of 1 $\mu$s in duration, with a typical pulse energy of between 80 and 100 mJ. During laser recanalization, progress of the ball was monitored by C-arm fluoroscopy After crossing the lesion, the channel was augmented by balloon dilatation as the device was withdrawn. At this point further angiography was performed to check the adequacy of the neolumen and to examine the run-off vessels. Spasm, if present, was treated by intra-arterial glyceryl trinitrate, and any areas of residual disease were retreated with further dilatation. When a satisfactory appearance was observed, the device was withdrawn and the arteriotomy and wound were closed Tibial vessels were treated where no obvious run-off vessel was visible on angiography. However, no attempt was made to treat occluded tibial vessels if a single patent vessel could be identified and a patent pedal arch was demonstrated on Doppler ultrasonographic examination

Patients were mobilized on the day after surgery. If the ABPI and clinical appearance of the limb were satisfactory after operation, the patient was allowed home after 3 or 4 days

Before discharge each patient underwent exercise testing and duplex scanning to examine the recanalized segment. Patients were followed up at intervals of 2 weeks for 1 month, at intervals of 1 month for 3 months, and then at intervals of 3 months for 1 year. After this they were seen every 6 months Exercise testing was carried out at each visit, with duplex scanning at 1, 3, 6 and 12 months, and thereafter annually

Arteries were considered to have reoccluded if symptoms returned or if the ABPI fell to within 0·15 of the preoperative level At this point patients had a further duplex scan, and arteriography if further intervention was contemplated Those requiring further intervention, for example percutaneous transluminal angioplasty, were considered failures of treatment, even if total reocclusion had not occurred. Evidence of reocclusion on duplex scanning was regarded as treatment failure.

Statistical analysis was carried out using *t* tests for normally distributed data. Grouped data were analysed by Fisher's exact test. Significance was set at $P < 0{\cdot}05$.

## Results

In 71 patients technical success was achieved in 58 of 78 limbs (74 per cent), with clinical success in 46 (59 per cent) The procedure was more successful in shorter occlusions (*Table 1*), except in those of 7–10 cm in length. This latter group had the second highest incidence of calcification, at 44 per cent, after the group with occlusions of less than 3 cm in length in which one of two lesions was markedly calcified. The results were better in non-calcified arteries than in calcified ones (*Table 2*)

The resting ABPI rose from a mean(s.d.) value before operation of 0·52(0·19) to 0·83(0·26) after operation and before discharge from hospital ($P < 0{\cdot}001$, Student's paired *t* test).

Technical failure occurred in 20 limbs. The main cause was

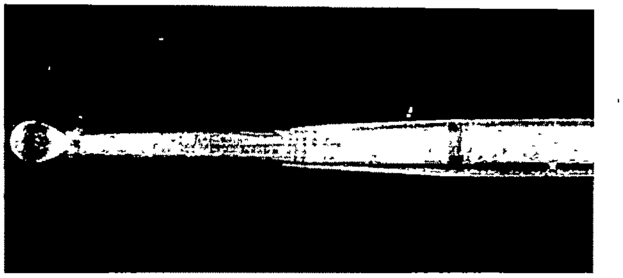

**Figure 3** *Ball-tipped optical fibre within a balloon angioplasty catheter*

**Table 2** *Results of laser-assisted angioplasty*

| | Median occlusion length (cm) | Technical success | Clinical success |
|---|---|---|---|
| Non-calcified | 21·5 (0·5–44) | 47 (84)* | 37 (66)† |
| Calcified | 15·5 (2–58) | 11 (50) | 9 (41) |
| Total | 18·0 (0·5–58) | 58 (74) | 46 (59) |

Values in parentheses are ranges and percentages. $^{*}P < 0·01$; $^{\dagger}P < 0·05$ (both non-calcified *versus* calcified, Fisher's exact test)

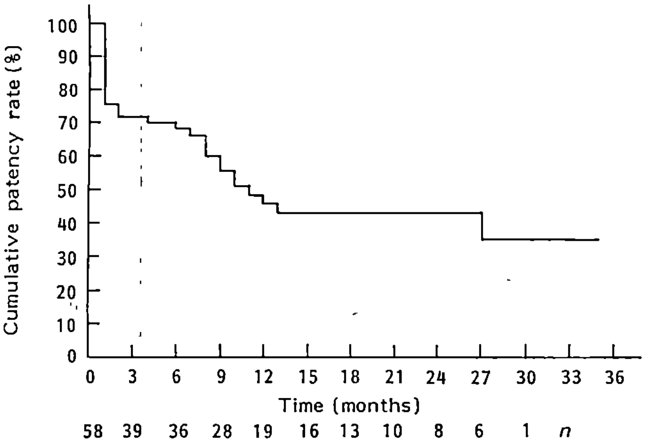

**Figure 4** *Life-table showing cumulative vessel patency rate following technically successful laser-assisted angioplasty. Numbers refer to limbs remaining at each time period*

dissection (15 cases), resulting in technical failure in ten. In ten of these 15 cases there was evidence of marked calcification, with dissection occurring at the point of calcification. In eight of the calcified cases, dissection resulted in technical failure. Perforation occurred in eight instances, leading to failure of the procedure in four In the other cases, contrast extravasation was noted. In three cases a retrograde approach was adopted with successful recanalization. In the remaining case, withdrawal and reintroduction of the delivery device resulted in a successful outcome.

There were four instances of the ball-tip breaking away from the fibre, all associated with the use of a percutaneous introducer sheath. The breakage occurred at the neck between ball and fibre while the ball was being withdrawn through the sheath. Although fused silica optical fibres are strong under compression, they are weak under extension, especially if coupled with sharp angulation. Breakage was especially likely to occur if the patient was obese, or if the percutaneous approach was steeply angled. In none of the cases could the ball be retrieved percutaneously. At the first occurrence an immediate check angiogram was normal, the lost ball was not identified, and the artery remained patent at 13 months. In two cases the ball lodged in the mid superficial femoral artery; both patients had femoropopliteal bypass. In the fourth case the ball was retrieved with an embolectomy catheter and the artery remained patent until the patient's death at 3 months from myocardial infarction. Although we now have more confidence in using the ball-tipped device percutaneously, early difficulties partly account for the preponderance of cut-down procedures.

Follow-up in technically successful cases ranged from 1 to 35 months, with a mean of 10 months. The cumulative patency rate for these technically successful cases was 67 per cent at 6 months, 45 per cent at 12 months and 42 per cent at 18 months (*Figure 4*). Patency rates for all 78 limbs were 37 per cent at 6 months, 25 per cent at 12 months and 23 per cent at 18 months.

In non-calcified vessels, the cumulative patency rate was 71 per cent at 6 months and 47 per cent at 1 year. For calcified vessels the corresponding figures were 47 and 35 per cent respectively, although the numbers at 1 year were very small (*Figure 5*). These differences were not statistically significant using the log rank test.

Patency was adversely affected by lack of run-off vessels, which is similar to the results obtained following surgical bypass. The patency rate was 58 per cent at 6 months and 38 per cent at 12 months in those with less than a two-vessel run-off. Corresponding figures for those with two or more patent tibial arteries were 76 and 54 per cent. These differences failed to reach statistical significance (*Figure 6*).

During follow-up, duplex scanning detected evidence of 50 per cent restenosis or more, measured by increased peak systolic velocity, in 12 limbs. This was not counted as treatment failure, because the natural history of this situation has not been established. Nine arteries with these changes on duplex scanning have remained patent for periods in excess of 18 months.

During the period of the study, a total of 25 limbs have reoccluded; 21 further procedures have been carried out in 12 of these reoccluded limbs. Nine limbs have come to eventual major amputation, for unsalvageable ischaemia in eight and as a life-saving procedure to eliminate a septicaemic focus in one. In three cases, bypass grafting was not feasible following failure of laser-assisted angioplasty.

In this series, a total of 19 limbs (24 per cent) underwent grafting. Operative reconstruction was performed in 11 limbs following failed laser angioplasty and in eight limbs that reoccluded following successful recanalization. Amputation

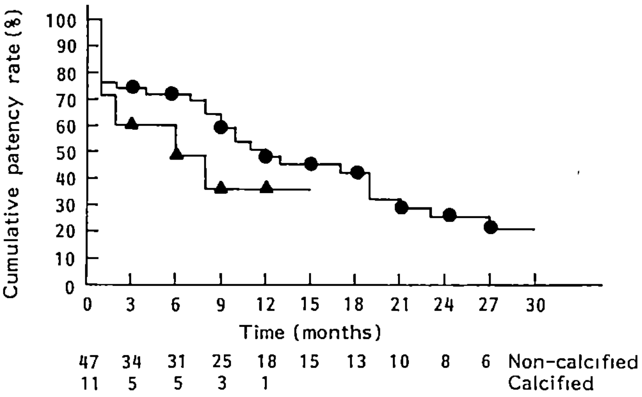

**Figure 5** *Life-table showing cumulative vessel patency rate in calcified (▲) and non-calcified (●) vessels following technically successful laser angioplasty. Numbers refer to limbs remaining at each time period*

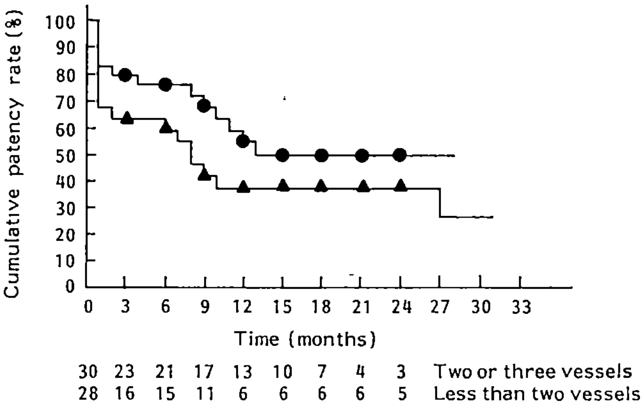

**Figure 6** *Life-table showing the effect of run-off vessels on cumulative vessel patency rate following technically successful laser angioplasty.* ●*, Two or three vessels,* ▲*, less than two vessels. Numbers refer to limbs remaining at each time period*

without prior grafting was carried out on four occasions, three following reocclusion and one after technical failure. In addition, four limbs underwent percutaneous transluminal angioplasty for symptomatic restenosis and three were relasered, all successfully. At the present time 32 per cent of patients have a patent artery at the site of laser-assisted angioplasty after a single procedure.

A total of ten patients (14 per cent) are known to have died. There were two perioperative deaths (3 per cent) One occurred from myocardial infarction 10 days after successful aortobifemoral grafting and laser angioplasty in a 71-year-old man. The other death was of a man of 74 years with severe chronic obstructive airway disease; he died from respiratory failure despite a successful procedure carried out percutaneously under local anaesthesia. The remaining deaths were due to myocardial infarction in seven cases and rupture of an abdominal aortic aneurysm in one.

## Discussion

This series demonstrates that laser-assisted angioplasty is capable of recanalizing long arterial occlusions of the lower limb arteries. The results showed a trend to decreased success with increased length of occlusion, although the results for those with occlusions of 7–10 cm were worse than for any other subgroup. The reason for this is not clear, although there was a high rate of arterial calcification in this group and one patient had $\beta$-thalassaemia and sickle cell disease, requiring exchange transfusion before operation. This patient was successfully recanalized, but reoccluded after operation. However, the group with 10–20 cm occlusions had a similar rate of calcification with a much higher success rate. It may be that this discrepancy is a chance finding that will disappear as numbers increase.

Although the success of the procedure was not as impressive as surgical bypass, the majority of patients in this series would have had to undergo bypass even if percutaneous transluminal angioplasty had been attempted first. Only 28 per cent of occlusions were less than 10 cm long and in longer occlusions transluminal angioplasty is associated with a high likelihood of failure[5,6]. Recent series reporting improved success in longer occlusions have avoided including those over 10 cm in length[26] In this series, 72 per cent of occlusions were longer than 10 cm. Although a cut-down procedure was required in the majority, this was in large part due to the initial work being done by vascular surgeons We now increasingly use a percutaneous approach and foresee this becoming the approach of choice, especially as more versatile delivery devices are developed.

Nine patients had amputations in this series, giving a limb salvage rate in those presenting with rest pain or tissue loss of 80 per cent. There was no significant difference in the amputation rate between the groups with successful and unsuccessful laser recanalization, although a larger number of amputations were subsequently undertaken in the former group In no case did the performance of a laser procedure preclude subsequent bypass grafting

The failure of laser-assisted angioplasty in calcified arteries conflicts with previous *in vitro* data showing that calcified plaque could be preferentially ablated by the pulsed dye laser using cleaved optical fibres with very high irradiance[20,22]. More recently we examined the ablation of calcified plaque with the newer ball-tipped devices and multifibre catheters, and found that although shattering of plaque could be achieved, crater formation was rarely accomplished at currently used pulse powers[27]. In addition we have noted that the commonest cause of failure is dissection immediately upstream of the calcified plaque Intraoperative duplex scanning has demonstrated that the plaque is lifted by the device during lasing. We feel that the change in plaque elasticity from an area of relatively soft plaque to one of much firmer consistency may set up stresses in the boundary region This may account for the tendency for dissection to occur at this point

Perforation occurred in eight patients The only evidence of haematoma formation was in a limb that was subsequently successfully treated, in which a popliteal fossa haematoma resulted following a small perforation of the popliteal artery. Perforation occurred commonly at the level of the adductor hiatus. It is at this point that the course of the superficial femoral artery curves as it passes into the popliteal fossa and is constrained in its movement by surrounding tendons. The adductor hiatus may also coincide with the point of maximal disease. Because this was also the commonest area to encounter dissection, we feel that improvements in delivery device design, allowing angulation of the tip, may well improve the technical success rate of this procedure.

Failure of the delivery device has occurred only in combination with the use of percutaneous introducer sheaths, and is related to sharp angulation of the sheath at the point where it enters the artery. To reduce this problem we were careful to keep the angle of approach of the percutaneous introducer to a minimum and to withdraw the ball-tipped fibre into the percutaneous sheath before removing both together at the end of the procedure.

Using current techniques and antithrombotic measures, the restenosis rate appeared to be worse than that seen after standard percutaneous transluminal angioplasty in shorter lesions[3,5], although better than that described for long arterial stenoses[28] We feel that this relates to the injury caused by balloon dilatation over a more extensive area of vessel wall. In published laser angioplasty series, using different delivery devices with long lesions, the results are similar to our own[13,29].

Experimental work has suggested that the platelet response and subsequent restenosis rates following stand-alone laser procedures (i.e. without the need for balloon dilatation) may be reduced by the hot-tip device or by the newer Excimer lasers[30,31]. This may relate more to the ability of lasers to recanalize arteries without splitting plaque[32] than to any difference in the thrombogenic properties of the treated vessel wall Further work is required to determine the rates of restenosis following laser angioplasty without adjunctive balloon dilatation.

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# Announcement

## International Hepato-Biliary-Pancreatic Association Frank Glenn Travelling Fellowship 1992

The International Hepato-Biliary-Pancreatic Association invites applications for the above travelling Fellowship. A stipend of US $5000 is available to subsidize a young investigator in the field of hepatobiliary and pancreatic disorders. The applicant must be sponsored by a member of the Association. The stipend may be used to support a laboratory project and/or to subsidize travel expenses which are deemed appropriate to the field of investigation. Applicants must be under 40 years of age and should have an established record of at least one or several papers concerning liver, biliary or pancreatic disease.

Applications should be made in writing and should include the following:

1. a copy of the applicant's curriculum vitae,
2. a summary of 1–2 pages of a research protocol describing how the stipend is to be used;
3. a letter of nomination from a member of the IHBP Association or your Department Chairman.

Applications should be sent to: Dr Haile T Debas, University of California, San Francisco, Department of Surgery, San Francisco, CA 94143-0104, USA by 30 April 1992 Telephone· (415) 476-1236 Facsimile (415) 476-1734.

Br. J. Surg. 1992, Vol. 79, January,
86–88

# Low-dose intra-arterial thrombolysis in the treatment of occluded vascular grafts

*As the use of intra-arterial thrombolysis increases, its application to specific areas requires definition. The results of treatment of occluded vascular grafts are presented. Thrombolysis using streptokinase or tissue plasminogen activator was planned in the treatment of 18 occluded vascular grafts (five aortofemoral bifurcation grafts and 13 infrainguinal grafts). Two patients, both with infrainguinal occlusions, did not receive thrombolytic therapy and were considered failures of treatment. Successful lysis occurred in three of five aortofemoral grafts, in both infrainguinal vein grafts and in five of nine infrainguinal synthetic grafts. The overall success rate was approximately 60 per cent. Two-thirds of the patients required no intervention following successful lysis. Percutaneous transluminal angioplasty was not found to be a useful additional procedure. A review of the literature revealed that intra-arterial thrombolysis is significantly more successful in the treatment of suprainguinal graft occlusion than in infrainguinal occlusions, there being no difference between infrainguinal vein and synthetic grafts. Provided that the limb is viable and there are no contraindications, intra-arterial thrombolysis is a useful means of clearing occluded grafts.*

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In addition to advice concerning smoking, several ways of maintaining graft patency have been suggested. These include the use of antiplatelet agents or anticoagulants[1,2] and the combination of distal vein grafts with arteriovenous fistulae[3] and distal polytetrafluoroethylene (PTFE) grafts with vein cuffs[4]. Furthermore, surveillance of vein grafts using duplex scanning, ankle arterial pressures at rest or after stress, or intravenous or intra-arterial digital subtraction angiography has been shown to detect asymptomatic stenoses which can be dealt with before the vein graft occludes[5,6].

Despite these measures there is still a significant incidence of graft occlusion. This applies particularly to grafts below the inguinal ligament, less so to aortoiliac grafts. Femoropopliteal bypass grafts fail at a rate of 17–22 per cent in the first year and 7–12 per cent per annum for subsequent years, depending on such factors as the nature of the graft material and the state of the distal run-off[7]. A recent survey revealed that 43 per cent of vascular surgeons felt that intra-arterial thrombolysis may have a role in the treatment of graft occlusion[8]. This paper describes an experience using low-dose intra-arterial thrombolysis in the treatment of occluded grafts

## Patients and methods

Of 101 patients with 112 ischaemic limbs who were considered for thrombolysis between November 1988 and February 1991, 18 had occluded grafts. In two patients the planned lysis was abandoned before treatment could start: one patient suffered a cerebrovascular accident during angiography, and the graft could not be cannulated in the other. These two patients are not considered further.

Patients were selected if they had either acute or chronic symptoms of graft thrombosis and there were no contraindications to thrombolysis. Any patient with a history of cerebrovascular accident within 6 months, dyspepsia, haemorrhagic problems or a recent operation was excluded.

Twelve patients received streptokinase (current dosage 5000 units/h) and four patients received recombinant human tissue type plasminogen activator (tPA, Boehringer Ingelheim, Bracknell, UK), 0.5 mg/h. The drug was given as a continuous infusion through a 5–7 Fr cannula inserted under local anaesthesia by a radiologist[9,10]. Subsequent angiography was carried out at intervals of 8–12 h. Catheter manipulations were performed, if necessary, at that time. On average, four visits to the radiology department for angiography were required[10]. Infusion was continued until lysis was complete or until there was no progression of lysis. Treatment was stopped if significant complications occurred. It is sometimes impossible to place the perfusing catheter into the thrombus initially. In such cases the catheter is placed against the thrombus and the infusion is started. This generally results in the thrombus softening so that the catheter can be advanced into it.

Of those patients with infrainguinal grafts, the indication for the original operation was rest pain in three and incapacitating claudication in eight. Two patients had no calf vessels demonstrated on arteriography, the remainder had two fair vessels. The aortic reconstructions were for claudication except in one patient who presented with a ruptured abdominal aortic aneurysm.

The median age of the patients at the time of the graft occlusion was 68 (range 42–89) years. Ten of the 18 patients whom it was our intention to treat suffered from incapacitating claudication and eight had rest pain. The median time to presentation from the onset of symptoms was 1 month (range from 4 days to 6 months). There were five aortofemoral bifurcation grafts, ten femoropopliteal grafts, two popliteal grafts and one femorotibial bypass graft. The median time to occlusion was 7 months (range from 1 month to 10 years).

Access to the occluded graft was attempted through the left axillary artery in seven cases, through the contralateral femoral artery in four and through the ipsilateral femoral artery in seven.

## Results

Lysis was successful in clearing ten of the 16 grafts treated and appeared to be more effective if thrombosis was recent. This correlates well with our experience of treating native artery occlusion[9,10]. The details of the patients successfully treated are summarized in *Table 1*. All of the five bifurcation grafts had single limb occlusions. Three occlusions were successfully cleared and none needed further treatment.

Of the distal grafts, the two vein grafts were successfully cleared. However, in one case no run-off was demonstrated and despite exploration of the calf vessels an amputation was ultimately performed. The other graft rethrombosed within 3 days and was treated by thrombectomy and refashioning of the distal anastomosis. Five of the nine infrainguinal synthetic

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**Table 1** *Details of patients who underwent successful thrombolysis*

| Patient no | Sex | Age (years) | Site of occlusion | Time since graft insertion (months) | Duration and nature of symptoms | Access | Agent | Further procedure | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 66 | Right limb AFBG | 60 | 6 weeks (IC) | Left axillary artery | SK | | Asymptomatic at 8 months |
| 2 | M | 54 | Right limb AFBG | 3 | 1 week (IC) | Left axillary artery | SK | | Asymptomatic at 8 months |
| 3 | M | 60 | Left limb AFBG | 14 | 3 months (IC) | Left axillary artery | tPA | | Asymptomatic at 8 months |
| 4 | F | 69 | Femoropopliteal (vein) | 2 | 1 month (RP) | Contralateral femoral artery | SK | Refashion distal anastomosis | Rethrombosed |
| 5 | F | 75 | Femoropopliteal (Dacron) | 4 | 4 months (IC) | Ipsilateral femoral artery | SK | Angioplasty<br>Refashion distal anastomosis | Rethrombosed |
| 6 | M | 62 | Femoropopliteal (PTFE) | 2 | 1 month (IC) | Left axillary artery | SK | | Asymptomatic at 10 months |
| 7 | M | 70 | Femoropopliteal (PTFE) | 2 | 4 days (RP) | Left axillary artery | tPA | Refashion distal anastomosis (*Figure 1*) | Asymptomatic at 10 months |
| 8 | M | 65 | Femoropopliteal (PTFE) | 2 | 1 month (RP) | Contralateral femoral artery | SK | | Rethrombosed at 3 months<br>Thrombectomy<br>Asymptomatic at 14 months |
| 9 | M | 65 | Popliteal bypass (vein) | 120 | 1 month (RP) | Ipsilateral femoral artery | SK | Run-off explored | Above-knee amputation |
| 10 | M | 67 | Popliteal bypass (PTFE) | 8 | 1 day (IC) | Ipsilateral femoral artery | tPA | | Asymptomatic at 10 months |

AFBG, aortofemoral bypass graft, PTFE, polytetrafluoroethylene, IC, intermittent claudication, RP, rest pain, SK, streptokinase, tPA, recombinant tissue plasminogen activator

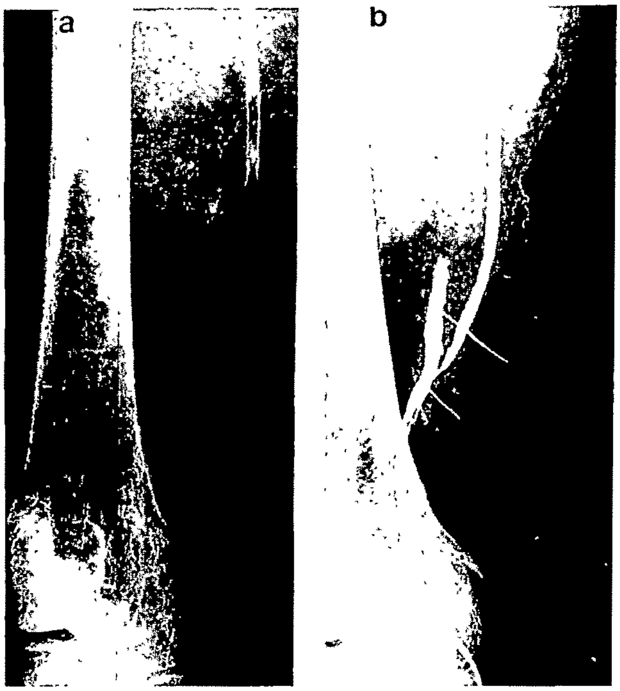

**Figure 1** *Arteriograms from a 70-year-old man who presented with an occluded femoropopliteal polytetrafluoroethylene graft causing rest pain* **a** *The initial arteriogram confirmed that the graft had thrombosed* **b** *Intra-arterial thrombolysis with recombinant tissue plasminogen activator cleared the graft in 24 h, revealing a distal anastomotic stricture which was corrected at operation*

grafts treated (PTFE, seven cases; Dacron® (E I du Pont, Wilmington, Delaware, USA), two cases) were successfully cleared Subsequently, two required surgical correction of distal anastomotic stenoses, one following unsuccessful angioplasty These stenoses were successfully demonstrated angiographically following lysis of the thrombus The other three occluded grafts had no identifiable stenoses and required no further treatment.

Six of ten successfully lysed grafts required no treatment other than lysis, there being no obvious cause for the graft thrombosis Of these six, one rethrombosed 3 months later and was successfully treated by thrombectomy The remaining five patients have patent grafts at a median of 8 (range 8–10) months after treatment.

Where lysis was unsuccessful, five patients had operative intervention and one had a chemical sympathectomy.

Complications included two gastrointestinal haemorrhages, both were minor in nature, neither patient becoming hypotensive or requiring transfusion Gastric and duodenal erosions were responsible and were treated conservatively. Five haematomas occurred, three axillary and two inguinal. Presumably the looser connective tissue in the axilla predisposes to haematoma formation. One patient had a large acute retroperitoneal haemorrhage due to bleeding extending proximally from a high common femoral puncture site. Direct suture of the puncture site was required Subsequent thrombectomy was required in this case for the graft occlusion There was one mild allergic reaction to streptokinase None of the patients died.

## Discussion

Failure of a graft within the first month after insertion is usually regarded as being due to technical reasons, either poor surgical technique or inappropriate choice of operation Late failure, i.e. that occurring after 1 year, is generally thought to be due to progression of atheromatous disease. Failure at an intermediate time is frequently due to neointimal hyperplasia leading to stricture This may occur at the distal anastomosis or, in the case of a vein graft, within the graft itself[11,12]. However, there is sometimes no cause related to the graft. Patient no 10, for example, had spent 3 h gardening in a crouched position before noting that his leg had become painful Presumably the graft had thrombosed owing to a kink causing temporary mechanical obstruction

When a graft has thrombosed the options available are conservative treatment, thrombectomy, graft revision or thrombolysis. The last has the advantage that it may clarify

**Table 2** *Results of attempted thrombolysis of occluded vascular grafts*

| | *n* | Successful lysis (%) | Reference |
|---|---|---|---|
| Suprainguinal | 56 | 77 | 13, 14, 20–26 |
| Infrainguinal | | | |
| Synthetic | 152 | 63 | 21–24, 26–31 |
| Vein | 114 | 64 | 13, 20–24, 28–33 |

the cause of the occlusion[13,14], allowing surgical or radiological correction. Of the present ten successfully cleared grafts, correctable lesions were found in three. Thrombectomy is a well established treatment, and in PTFE grafts aggressive reoperation can result in patency rates of 60 per cent at 2 years and 37 per cent at 5 years[15]. Complete graft revision is usually delayed until the original graft is no longer salvageable.

There is good evidence that thrombolysis may be successful in up to 80 per cent of occluded native arteries, with a low complication rate[9,10,16–18] By comparison, the overall success rate in the present series of occluded grafts was 60 per cent. Other authors have reported similar results[19–21] Suprainguinal grafts appear to be cleared more effectively by thrombolysis than infrainguinal grafts (*Table 2*). There seems to be no difference with respect to the chance of success between infrainguinal vein and synthetic grafts Of all the grafts treated in our series, approximately one-third required nothing other than thrombolysis to achieve satisfactory short-term results. It has been suggested that these grafts will rethrombose considerably sooner than those with an underlying correctable lesion A 6-month patency rate of 80 per cent in grafts with correctable stenosis has been reported, compared with only 10 per cent where any stenosis remains[20]

Thrombolysis is not without its problems. Complications are not uncommon: major haemorrhage occurs in 5 per cent of cases, minor haemorrhage in 15 per cent and stroke in 1 per cent[34]. Furthermore, the technique requires a large radiological effort[10].

Provided the limb is viable, graft thrombolysis is at least a useful first step in clearing an occlusion, and perhaps in defining the cause for it. In some cases it is all that is needed to establish long-term patency.

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# Correspondence

## Haemodynamic significance of calf veins

*Sir*
I read with interest the article by Zukowski and colleagues (*Br J Surg* 1991; **78**: 625–9) The role of calf perforating veins in the aetiology of venous hypertension remains the subject of controversy, and their paper demonstrates the difficulties encountered when addressing this issue.

The authors have assiduously investigated their patients using ascending phlebography, ambulatory venous pressure measurements and Doppler ultrasonography. On the basis of these investigations they have allocated patients to groups with superficial or deep venous insufficiency, with or without calf perforator incompetence Substantial reliance is placed on the accuracy with which these investigations distinguish between deep and superficial venous insufficiency. As the authors concede, to explain the findings obtained from venous pressure measurements in the groups with superficial venous disease and incompetent perforators, unidentified deep vein incompetence in the calf must be assumed. So the impression gained from the title of the article and abstract that the problems identified by the authors are attributable to calf perforating veins is a little misleading.

The study shows that in some patients with superficial venous disease and 'incompetent' perforating veins there is a severe functional deficit The only way to determine what the perforators alone contribute to this deficit would be to ligate them and repeat the investigation or, alternatively, to treat the superficial disease and assess the effect on venous function. I would be most interested to hear whether surgical treatment of this nature influenced the indices of venous function in these patients

It might have been better not to attribute the functional venous abnormalities to the perforating veins, as this may lead surgeons to assume that surgical ligation of these vessels will lead to improvement of the calf muscle pump. As the authors acknowledge, it is still unclear whether this procedure would be of benefit

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## Survival after local recurrence of soft tissue sarcoma

*Sir*
Barr *et al* (*Br J Surg* 1991; **78**: 648–50) discussed the influence of local recurrence upon the survival of patients with soft tissue sarcoma It is well known that patient survival is inversely proportional to the size of the primary tumour Patients who survive their original tumour without developing distant metastases may well be at risk for distant disease if the recurrence if appreciably larger than the primary. I have been describing tumour–host balance in these terms for over 10 years[1,2] Regrettably, most investigators fail to consider the sizes of primary and recurrent tumours when evaluating the influence of local recurrence on survival. Investigators should attempt to quantify the volume of both local and nodal recurrences in all patients with solid tumours.

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## Biliary bile acid profiles in familial adenomatous polyposis

*Sir*
The article by Spigelman *et al.* on biliary bile acids in patients with familial adenomatous polyposis (FAP) (*Br J Surg* 1991; **78**: 321–5) raises important questions. The differences in gallbladder bile acids could be due to increased deoxycholate absorption because of age[1] It is not clear whether patients undergoing cholecystectomy were included and the use of 3-day beating heart donors as 'controls' is dubious because of prolonged fasting.

The differences in duodenal bile acids could be due to colectomy rather than FAP since colectomies *per se* will result in increased faecal losses[2], increased primary bile acid synthesis, and increased loss of secondary bile acids[3] In health the ratio of chenodeoxycholate to cholate is near unity, since although chenodeoxycholate is better conserved than cholate[4], the synthesis of cholate is greater[5] Postcolectomy, the proportion of cholate must therefore increase, this is borne out by the reduction of taurine conjugates.

A favourable comparison with another study[6] must be questioned since gallbladder status was determined in only 14 per cent of patients with polyps and there was no polyp screening of 'controls'

A more accurate comparison is that between gallbladder bile acids from patients before colectomy with FAP and control duodenal bile acids[7]; in this case there is no difference between patients with FAP and 'controls'. Moreover, since patients with FAP continue to develop adenomas following colectomy, the lower chenodeoxycholate:cholate ratio in patients after colectomy appears at variance with previous work[8].

The use of biliary bile acid concentration is of little value because of numerous physiological variables affecting this and any errors will be accentuated by the inaccuracies of endoscopic duodenal bile collection.

Although differences in biliary bile acids of patients with FAP may exist, those in this study may be accounted for by known physiological variables; further study is therefore required.

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## Authors' reply

*Sir*

We are pleased with the interest generated by our paper on biliary bile acid profiles in familial adenomatous polyposis (FAP) Many explanations can be advanced to explain the observed differences; we propose some, Radley *et al* propose a number of others

In reply to their one query, the age-matched comparison between patients who had bile aspirated from the gallbladder excluded those control patients who had bile taken at the time of cholecystectomy for gallstones We otherwise simply reiterate that in patients with FAP. (1) upper gastrointestinal cancers and adenomas cluster around the ampulla of Vater[1], (2) when gastric adenomas are present, bile reflux into the stomach is more marked[2]; (3) there is an excess of DNA adducts in duodenal DNA (i e carcinogen-damaged DNA) compared with controls[3], and (4) the biliary bile acid profiles are abnormal[4]. All of this lends strong support to our contention that FAP bile is 'bad' bile.

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## Morbidity and function after colectomy with ileorectal anastomosis or restorative proctocolectomy for familial adenomatous polyposis

*Sir*

The article comparing restorative proctocolectomy (RPC) and ileorectal anastomosis as a treatment for familial adenomatous polyposis (FAP) by Madden and colleagues (*Br J Surg* 1991, **78** 789–92) is an important contribution to the literature

However, the findings of diminished libido in 11 per cent of the patients undergoing RPC merits further discussion It is surprising that only a minor degree of sexual dysfunction was detected in five of 99 patients following a major operative procedure The occurrence of sexual problems only in those patients undergoing RPC is significant and may indicate more serious sexual disorders In our experience, patients who suffer serious sexual problems, such as retrograde ejaculation and partial or complete impotence following rectal operations, are reluctant to disclose their problems, even after several interviews On occasions, patients have denied problems which they have admitted to their general practitioner We think it likely, therefore, that, in common with other publications, the incidence and severity of sexual dysfunction following RPC has been underestimated This is of particular concern when RPC is performed for FAP, as the creation of a sexual problem will not only affect the patient but may deter family members from attending for screening and subsequent treatment.

Unfortunately, RPC is often performed for FAP in a less discriminatory manner than that practised by the authors, and we are concerned this may have an adverse affect on screening protocols for this disease. The authors' advice that RPC should be restricted to those patients where there is a high risk of developing rectal cancer is, therefore, particularly important

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## Suture technique and perianastomotic tumours

*Sir*

I enjoyed the article by O'Donnell *et al* (*Br J Surg* 1991; **78**. 671–4) on suture technique and anastomotic carcinogenesis. Evidence is now accumulating that sutures themselves can enhance tumour formation at an anastomosis over and above the enhancement caused by a healing wound In this Department, recent work with carcinogen has shown that anastomotic tumours developed in 41 per cent of a sutureless group ($n = 32$) compared with 68 per cent of a sutured group ($n = 99$) ($P < 0{\cdot}02$). Furthermore the proportion of tumours occurring at the anastomosis was greater in the sutured group This work plus the findings of O'Donnell *et al.* suggest that the crucial factor would appear to be the interaction of sutures with the mucosa.

I have just a couple of minor criticisms No comment was made regarding the presence or absence of tumour at the anastomoses that underwent bromodeoxyuridine labelling. The elevated labelling index in the transmural suture group may thus have been a reflection of an increased number of tumours and cannot be attributed directly to the sutures themselves. particularly as the majority of investigators have suggested that indices of cell turnover return to normal 4–12 weeks after anastomosis or suture placement[1–3] However, recent results in our own laboratory have shown that crypt cell production rates (CCPRs) are significantly elevated at sutured anastomoses compared with adjacent descending colon for at least 3 months after operation whereas the CCPR is normal at sutureless anastomoses by 1 month

One final, perhaps pedantic point, is that the authors should be wary of the assumption that an elevated labelling index necessarily translates into increased cellular proliferation, without knowledge of what happens to the cell cycle duration or crypt size

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## Thyroglossal duct cyst carcinoma

*Sir*

With regard to the paper by Weiss and Orlich (*Br J Surg* 1991, **78**: 87–9), I would like to point out that there has been another report of two cases published by us (Thyroglossal duct cyst carcinoma *Am Surg* 1988, **54** 315–17) Thus the total number of cases should be 117. Another matter that deserves attention is the surgical approach for the disease. The authors state that Sistrunk's operation should be sufficient for non-metastatic disease, yet their own patient was readmitted and underwent a near total thyroidectomy when the diagnosis of malignancy was established, despite the normal appearance of the thyroid gland and cervical nodes. According to our experience, limited as it may be, Sistrunk's operation should suffice for such cases.

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## Selective uptake of glutamine in the gastrointestinal tract

*Sir*

The recent article by McAnena *et al* (*Br J Surg* 1991; **78** 480–2) has provided some additional and useful new data supporting the selective uptake of glutamine by the gut in critically ill patients. However, I would like to comment on a statement which appeared in the abstract of the article· 'This has significant implications as glutamine is not provided in most commercially available parenteral and enteral nutrition formulations '

It is true that parenteral nutrition formulae do not include glutamine due to its degradation to glutamic acid, ammonia, and pyroglutamic acid (5-oxoproline, 2-pyrrolidone-5-carboxylic acid) in solution[1] In contrast, all enteral formulae that contain food proteins contain glutamine. As an amino acid, glutamine is a 'natural' component of food protein and is found in quantities proportional to the amount of protein ingested. It is estimated that glutamine is approximately 5–10 per cent of the total protein[2,3] Enteral feedings are generally the preferred method of providing calories and protein to patients who require nutritional support. Glutamine and glutamate are abundant and efficient fuels present in nearly all dietary protein and together comprise approximately 30 per cent of the amino acid nitrogen in meat[2]. A protein meal, therefore, is rich in intestinal fuels

Unlike parenteral amino acid regimens, synthetic elemental diets (amino acids, peptide and protein containing) may provide key intestinal substrates to hospitalized patients This information provides a biochemical rationale, in part, for the use of enteral as opposed to parenteral feedings whenever possible Total parenteral nutrition feeding results in villus atrophy, a phenomenon that is generally reversible when oral feedings are resumed. Based on the evidence for an intestinal glutamine requirement, it is reasonable to suggest that long-term parenteral feeding regimens may provide inadequate substrate to nourish the gut. Glutamine is not a constituent of commercially available parenteral nutrition solutions. Hence, glutamine for the gastrointestinal tract must be derived from synthetic pathways in other tissues.

To date, findings suggest that glutamine is a preferred gut fuel Although glutamine is considered a nutritionally non-essential amino acid, there are data supporting its role as a conditionally essential nutrient in some stress states. Glutamine may be involved in intestinal adaptation and in maintenance of the gut barrier to bacterial translocation[4,5]. Whether the amount found in the protein of an enteral formula is adequate for the hospitalized patient still needs further research[6]. It is unclear whether glutamine must be provided to the patient in a free form (crystalline amino acid) or bound form in order to extend the beneficial effect to the gastrointestinal tract It seems logical that glutamine in any form (free, bound in protein, bound in hydrolysates) would be beneficial to the gut in maintaining and restoring integrity. Further research is needed to elucidate the mechanism and verify these early results

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## Regeneration of the spleen and splenic autotransplantation

*Sir*

We read with great interest the review by Holdsworth on the regeneration of the spleen and splenic autotransplantation (*Br J Surg* 1991; **78** 270–8). This is indeed a controversial field, not surprisingly we stressed different aspects in our own review[1] Some aspects are of general importance

First, Holdsworth states that immunohistological studies have never been undertaken on regenerated spleens On the contrary, monoclonal antibodies against T lymphocytes and splenic macrophages have been used to show the sequence of the development of splenic compartments[2], and the size of the compartments has been quantified by morphometry[3] The red pulp is formed first Then the white pulp develops with the periarteriolar lymphatic sheath first, then follicles, and finally the marginal zone[1,2] There is growing evidence that the different splenic compartments have specific immunological functions[4] and that the marginal zone plays an essential role in immune reactions against thymus-independent type 2 antigens, such as pneumococcal antigens[5].

Second, Holdsworth mentions alterations in lymphocyte subsets in the peripheral blood after splenectomy These changes are not surprising because the spleen is the most important organ in lymphocyte recirculation[6] and splenic tissue also influences the migration pattern of lymphocyte subsets in other lymphoid organs[7]

Third, splenic regeneration is largely dependent on age. The increase in splenic weight and blood flow[8] and the immunohistological regeneration[2] of splenic tissue is much better when splenic tissue is transplanted in newborn on weanling rats compared with adult rats. The protective function in rats infected with pneumococci was evident only when splenic tissue was transplanted in neonatal animals[9] We would suggest that splenic regeneration might be much more effective in children than in adults

Last, the clinical role of splenic autotransplantation is still under debate Because of the small numbers of patients in each individual clinic, we would recommend international multicentre cooperation to evaluate the clinical benefits of autotransplanted splenic tissue in patients of different ages

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## Emergency laparotomy in patients with AIDS

*Sir*

I read with interest the article by Davidson and colleagues (*Br J Surg* 1991, **78**: 924–6) I must commend the authors on their accumulation of 28 AIDS patients who had undergone emergency laparotomy. There are several important points which need to be clarified When we reported what remains the largest series of emergency colectomies for cytomegalovirus ileocolitis in AIDS patients, none of the patients had received preoperative anti-HIV therapy such as Zidovudine, anti-CMV therapy such as Foscarnet or Ganciclovir, or antiherpes therapy such as Acyclovir (*Dis Colon Rectum* 1988; **31** 755–61). This is in strong contradistinction to the series by Davidson and colleagues in which 12 patients received anti-HIV therapy and four patients received antiherpetic therapy. More important, all seven patients with known or suspected CMV infection apparently received anti-CMV therapy before surgical intervention. These differences alone may well account for the differences in mortality rates at one month, which were 71 per cent in our series and 11 per cent in the current Davidson series. However, this difference appears to decrease at 6 months as our mortality rate was 86 per cent whereas the mortality rate in Davidson's series was 52 per cent This difference seems much less dramatic As pointed out by Davidson and co-workers, other authors have reported results identical to those of our 1988 study (*Ann Surg* 1989; **210**: 428–33, *Arch Surg* 1988, **122**: 170–5; *Dig Dis Sci* 1988; **33**: 741–50). Therefore, the improved survival reported by Davidson and associates may not be because of earlier surgical intervention or because of a change in our understanding of AIDS. Davidson and colleagues noted that 26 of their patients carried the diagnosis of AIDS before operation. This stands in strong contradistinction to our 1988 paper, in which only three patients were diagnosed before operation as having AIDS. Therefore, the improved survival noted by Davidson can be attributed to an earlier recognition of AIDS and an earlier commencement of medical management

As our medical armamentarium continues to increase and as more and more physicians become familiar with the various protean manifestations of AIDS, our success with the treatment of cytomegalovirus ileocolitis should improve even further

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## Abdominal cramp

*Sir*

Cramp of the abdominal wall muscles is a rare cause of abdominal pain simulating an acute abdomen, so I thought you might be interested to learn of my personal experience. I am a retired surgeon of 82 years and on a recent visit to Central Tibet (September 1990) returned overland to Nepal I was perfectly well during the two weeks in Tibet but found the last day exhausting as we had to walk/climb down steep rocky paths, because the road was blocked, to the bridge separating Tibet and Nepal There followed a four-hour jeep ride over a rough road to the mountain resort of Dhulakel (13716 metres) and a climb up steps, where after a drink of tea I retired to bed

A few minutes after resting on the bed, there was a sudden onset of excruciating abdominal pain and I felt a mass in the central abdomen. The very severe pain began to ease an hour or so later, when self-examination revealed not a mass but rigidity of the abdominal wall The local doctor came, made a cursory examination and gave an intramuscular injection of a strong analgesic drug and left another dose for injection and tablets About four hours later the abdominal pain had lessened and the whole right abdomen was soft, but the left abdomen remained rigid, the left rectus standing out like an iron bar Some hours later this rigidity had passed, leaving only the lateral muscles rigid, which felt like a mass Some 15 hours after the onset all rigidity and pain had gone, leaving the abdomen feeling sore and bruised, and myself weak

My first thought was a ruptured aorta, then a ruptured rectus muscle, then a perforation, and finally the correct diagnosis – a simple spasm of the abdominal muscles, that is cramp The attack had lasted about 15 hours The pain, at first unbearable, ceased once all the spasm had passed off, this spasm relaxing progressively from right to left

A review of text books and the literature and questioning surgical colleagues has not revealed any similar case Muscle spasm or cramp is a well known condition, rarely affecting abdominal muscles, and the cause is unknown[1–5] Cramp does occur in some neurological disorders and metabolic diseases, with certain drugs, and with muscular exertion, but usually there is no such relation This abdominal cramp was presumably related to unaccustomed exercise, though this was not unduly strenuous and I was not aware of unusual use of the abdominal muscles, only of the quadriceps.

There are few exact descriptions of cramp in the literature, probably because the condition is rarely observed by a doctor Abdominal cramp is described as occurring in heat cramp, the central abdominal muscles going into spasm first, so forming a discrete mass, before spreading to all the abdominal muscles; the attack may last 24 hours or longer However, Talbott in his classic article on heat cramp[1], says that attacks of cramp lasting many hours consist of repeated spasms each of a few minutes in duration, not one persistent spasm as in my case

I would be interested to hear from anyone who has knowledge or experience of this condition

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## Surgery for Crohn's disease in childhood

*Sir*

We were very interested to read the article by Davies and colleagues (*Br J Surg* 1990, **77**: 891–4) on surgery for Crohn's disease in childhood We were particularly interested in their classification of the site of disease Most large reviews of Crohn's disease have divided it into three – ileocolic, small intestinal and colonic[1,2]. Like Davies and colleagues, we too have just reviewed our results for surgery in Crohn's disease[3] Again like them we noted a significant number of cases (seven of 54) who had more extensive disease, required more operations and had more complications. Five of the seven had relapsed after a mean of 1 4 years and four had had further surgery These patients were more likely to present with abscesses or fistula formation.

In our paper we have termed this group 'jejuno–ileocolic', but it is obviously the same group which Davies and colleagues have called 'panenteric'. The choice of name does not matter. what does is the recognition of this category of Crohn's patients who appear to be more prone to many of the complications of this disease

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# Notices and announcements

13–15 February 1992
**Specialist Short Course: Medical Management of Major Incidents**
*London, UK*
*Information.* J Ashton, Wolfson Conference Centre, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

27–28 February 1992
**Surgical Masterclass on Endo-Anal Surgery for Consultant Surgeons**
*Edinburgh, UK*
*Information* Mrs Maureen Webb, Royal College of Surgeons of Edinburgh, Nicolson Street, Edinburgh EH8 9DW, UK

6 March 1992
**Symposium: A Reappraisal of Femoro-Distal Bypass Surgery**
*Liverpool, UK*
*Information* Mr P. L Harris, Department of Surgery, Broadgreen Hospital, Thomas Drive, Liverpool L14 3LB, UK

8–11 March 1992
**36th Annual Convention, American Institute of Ultrasound in Medicine**
*San Diego, California, USA*
*Information:* L E. Olech, 11200 Rockville Pike, Suite 205, Rockville, Maryland 20852-3139, USA

24 March 1992
**Study Day on Management of Pancreatic Cancer**
*Southampton, UK*
*Information* Mrs J Daniels, University Surgical Unit, F Level Centre Block, Southampton General Hospital, Tremona Road, Southampton SO9 4XY, UK

30 March–4 April 1992
**Head and Neck Oncology: Current Issues and Recent Advances**
*London, UK*
*Information* Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

1–3 April 1992
**Association of Surgeons of Great Britain and Ireland Annual Meeting**
*Jersey, UK*
*Information:* Ms Caroline Ross, The Royal College of Surgeons, 35/43 Lincoln's Inn Fields, London WC2A 3PN, UK

13–14 April 1992
**Injury Research Group 1992 Meeting**
*Manchester, UK*
*Information:* Dr R. N. Barton, North Western Injury Research Centre, Stopford Building, University of Manchester, Oxford Road, Manchester M13 9PT, UK

22–25 April 1992
**Updating Course on Pancreatic Diseases**
*Genoa, Italy*
*Information* Organizing Secretariat, QB Service, Via Visconti Venosta 4, 21122 Milano, Italy

22–25 April 1992
**2nd International Workshop and Symposium on Therapeutic Endoscopy and Gastroenterology**
*Shanghai, China*
*Information:* Dr J. W C. Yeung, Department of Medicine, Prince of Wales Hospital, Hong Kong

3–7 May 1992
**7th International Congress on Senology (Breast Diseases) of the Senological International Society**
*Rhodes, Greece*
*Information.* Congress Secretariat, 102 Michalakopoulou Street, GR-115 28 Athens, Greece

10–16 May 1992
**Acute Trauma Management**
*Belfast, UK*
*Information* Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

15 May 1992
**Abdominal Aortic Aneurysms – Assessment and Management**
*Ayr, UK*
*Information.* Mr G Stewart, The Ayr Hospital, Dallmington Road, Ayr KA6 6DX, UK

17–23 May 1992
**Recent Advances in Endocrinology and Metabolism**
*Edinburgh, UK*
*Information* Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

20–23 May 1992
**83rd Meeting of the American Association for Cancer Research**
*San Diego, California, USA*
*Information* American Association for Cancer Research, Inc., Public Ledger Building, 620 Chestnut Street, Suite 816, Philadelphia, PA 19106-3483, USA

27–29 May 1992
**European Council for Coloproctology Fourth Biennial Congress**
*Marseille, France*
*Information:* Patricia Vallet, Alice Congrés, 12 Cours Jean Ballard, BP 2028 13201 Marseille cedex 01, France

2–5 June 1992
**Eurochirurgie '92 2nd European Congress of Surgery**
*Brussels, Belgium*
*Information:* Congress Secretariat: Eurosurgery '92, Brussels International Trade Fair, Place de Belgique, B-1020 Brussels, Belgium

7–10 June 1992
**International Congress on Cancer of the Esophagus**
*Genoa, Italy*
*Information:* Secretariat, Luigina Bonelli, Unit of Clinical Epidemiology and Trials, Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy

7–11 June 1992
**4th World Congress of Hepato-Pancreato-Biliary Surgery**
*Hong Kong*
*Information* Secretariat, International Conference Consultants Ltd., Suits A and B, 16/F, Casey Building, 38 Lok Ku Rd, Sheung Wan, Hong Kong

9–10 June 1992
**Specialist Short Course: New Trends in Pathology**
*London, UK*
*Information* J Ashton, Wolfson Conference Centre, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

15–19 June 1992
**Specialist Short Course: Advances in Haematology**
*London, UK*
*Information.* J. Ashton, Wolfson Conference Centre, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

24–27 June 1992
**The Endocrine Society 74th Annual Meeting**
*San Antonio, Texas, USA*
*Information* Ann Singer, The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814, USA

28 June–3 July 1992
**4th Oxbridge Organ Transplantation Course**
*Cambridge, UK*
*Information:* Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

2–3 July 1992
**Surgical Research Society Meeting**
*Edinburgh, UK*
*Information* Professor J R. Farndon, Department of Surgery, Bristol Royal Infirmary, Bristol BS2 8HW, UK

5–10 July 1992
**Immunology and the Nervous System: Clinical Aspects**
*Oxford, UK*
*Information.* Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

2–4 September 1992
**Ultrasound Angiography '92**
*Southampton, UK*
*Information* Secretariat, Ultrasound Angiography '92, PO Box 15, Eastleigh, Hampshire SO5 5XG, UK

9–11 September 1992
**2nd Nottingham International Breast Cancer Meeting**
*Nottingham, UK*
*Information.* Mrs Wendy Bartlam, Professorial Unit of Surgery, City Hospital, Hucknall Road, Nottingham NG5 1PB, UK

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# The American Journal of Surgery®

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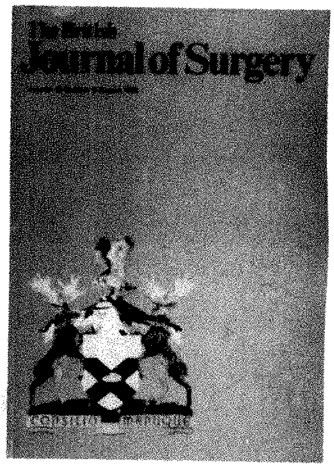

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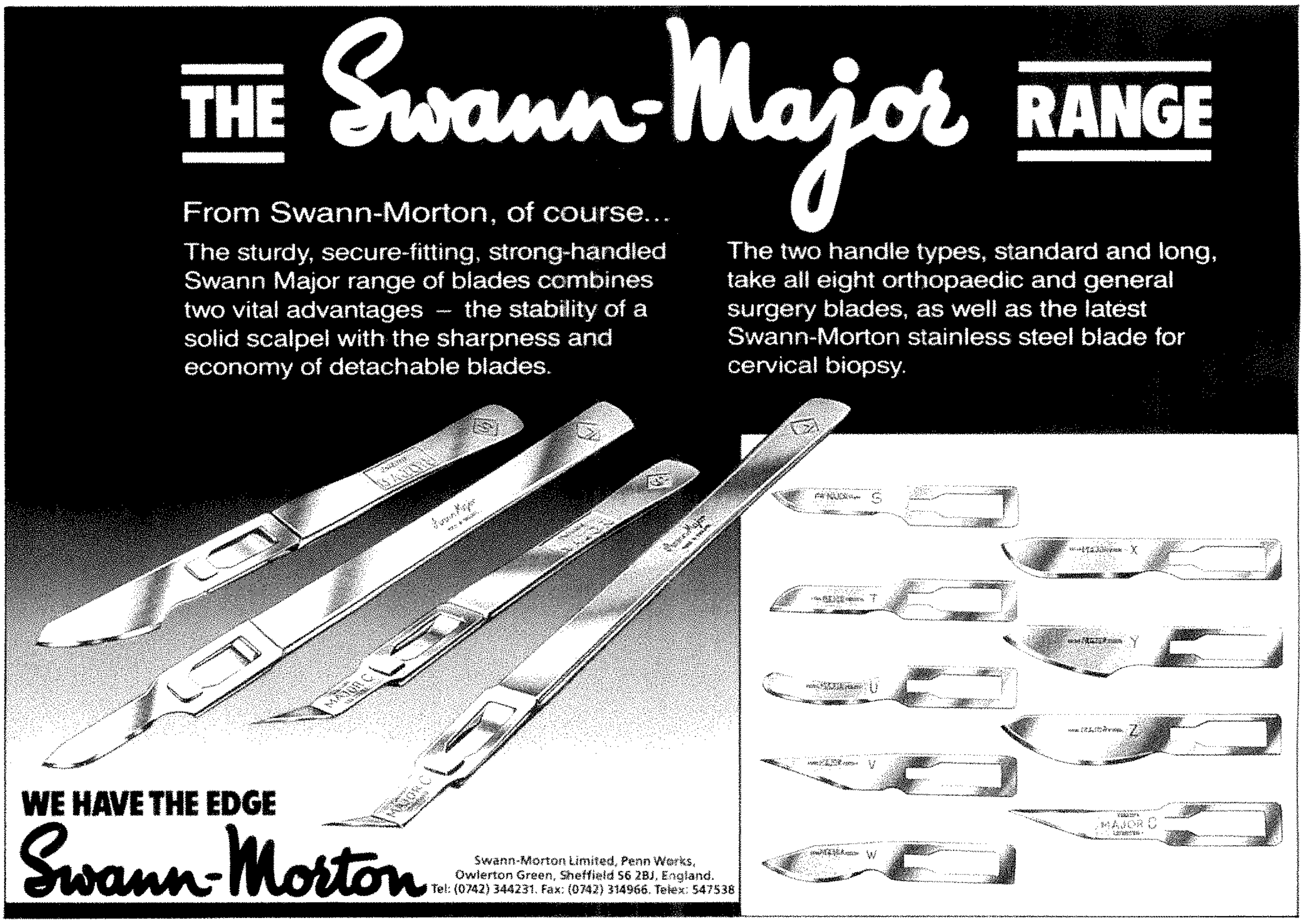

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# EUROSURGERY

## Promoting Research and Training in Surgery

## European Congress of Surgery

## 2–5 June 1992
## Brussels

**The Second European Congress of Surgery 'Eurosurgery 92' will take place in Brussels in June 1992.
This meeting will pursue the aims of Eurochirurgie/Eurosurgery to promote research and training in surgery.**

## Preliminary Scientific Programme

### I. General topics

| | |
|---|---|
| 2 June | What is new in European surgery?<br>Computers in clinical surgery<br>AIDS and surgery<br>New aspects of laser surgery |
| 3 June | Surgery in the aged |
| 4 June | War/tropical surgery<br>Ambulatory surgery<br>History of surgery |
| 5 June | Decision making in surgery<br>Theoretical surgery<br>Insurance implications in surgery<br>Stapling in surgery<br>Cost of surgical activity<br>Organization of the operative complex<br>Surgical nursing symposium |

### II. Abdominal and Oncological Surgery

| | |
|---|---|
| 2 June | Gastro-oesophageal reflux<br>Gastric stump cancer<br>Colon cancer<br>Hydatid cyst of the liver<br>Motility disorders of oesophagus |
| 3 June | Saving the spleen<br>Diverticulitis of the colon<br>Colonic volvulus<br>Laparoscopic cholecystectomy symposium<br>Prospects and future of laparoscopic surgery<br>Colon carcinogenesis |
| 4 June | Abdominal surgery by laparoscopy<br>Laparoscopic surgery: training<br>Cancer of the oesophagus<br>Oesophageal diseases<br>Reducing sepsis in colorectal surgery<br>Infections in abdominal surgery<br>Liver metastases<br>Hirschsprung's disease<br>Major hepatic surgery |
| 5 June | Acute pancreatitis<br>Radical surgery in rectal cancer<br>Adjuvant treatment in rectal cancer<br>Stoma therapy<br>Stapling in surgery |

### III. Training in Surgery

| | |
|---|---|
| 2 June | Specialisation in general surgery |
| 3 June | Training in surgery<br>Surgical training in Eastern Europe |
| 4 June | Laparoscopic surgical training<br>Surgical video session |

### IV. Transplantation Surgery

| | |
|---|---|
| 5 June | Multiorgan harvesting and preservation in Europe<br>Transplantation in Belgium<br>Immunosuppression regimens<br>Liver transplantation: new prospects |

### V. Traumatology and Orthopaedic Surgery

| | |
|---|---|
| 3 June | Saving the spleen |
| 4 June | Early management of multiple trauma<br>Arthroscopic surgery in 1992<br>Hand surgery<br>Treatment of major pelvic trauma |

### VI. Paediatric Surgery

| | |
|---|---|
| 4 June | Hirschsprung's disease |

### VII. Thoracic and Oncological Surgery

| | |
|---|---|
| 2 June | Early breast cancer<br>Gastro-oesophageal reflux<br>Oesophageal motility disorders |
| 3 June | Advanced breast cancer |
| 4 June | Lung metastases<br>Oesophageal diseases<br>Cancer of the oesophagus |
| 5 June | Stapling in surgery |

### VIII. Endocrine Surgery

| | |
|---|---|
| 3 June | Satellite disorders of hyperthyroidism |
| 5 June | Diagnosis and multimodal therapy of thyroid cancer |

### IX. Vascular Surgery

| | |
|---|---|
| 5 June | Endovascular surgical procedures<br>Abdominal aortic aneurysm<br>Prostheses in vascular surgery |

### X. Plastic Surgery

| | |
|---|---|
| 4 June | Burn injury<br>Microsurgery<br>Hand surgery<br>Malignant tumours of the face |

### XI. Gynaecological Surgery

| | |
|---|---|
| 3 June | Gynaecological laparoscopy |

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# The British Journal of Surgery

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## Cover picture

### The German Surgical Society (Deutsche Gesellschaft für Chirurgie)

For centuries surgery on the continent of Europe bore the stamp of the great French masters: Henry de Mondeville, Guy de Chauliac, Ambroise Paré and others. The first Germans of repute who published scientific treatises on the art of surgery in their mother tongue were Hans von Gersdorf (1517) and Lorenz Heister (1719).

In the eighteenth century surgical colleges were founded (Hannover, 1716; Berlin, 1726; Dresden, 1748; Mannheim, 1754 and others) for the training of a superior type of external barber surgeon, still strictly separate from the academic internists. The academic recognition of surgery was achieved in the nineteenth century with the foundation of university chairs within medical faculties

In March 1872, soon after unification of the German Reich, Bernhard von Langenbeck, Gustav Simon and Richard von Volkmann approached their surgical colleagues with their plan to found a society with an annual scientific meeting. The aim was to keep abreast of the rapid expansion of surgical science, to foster the personal exchange of ideas and to support common ventures. The response was overwhelming. By 1910 the membership roster exceeded 2000 names and before World War I the impact of the Deutsche Gesellschaft extended beyond the boundaries of Germany. Twenty per cent of the members came from Austria, German-speaking Switzerland, Russia, the Balkan states and Japan. They were joined by active and honorary members from Great Britain such as Sir James Paget, Lord Lister, Sir Spencer Wells and Sir Alexander Ogston (discoverer of *Staphylococcus* and pupil of Robert Koch).

After 1945 the German Surgical Society was divided, as was the old Reich, into two separate States. the Federal Republic and DDR. It took 4 years before the surviving West German surgeons could meet again in a circus tent in Frankfurt. It is particularly gratifying to know that many foreign colleagues – among them Sir Gordon Gordon-Taylor, Broster, Macintosh, Leriche and Fontaine – joined us to renew the international bonds of surgical friendship. In 1958 the Societé Internationale de Chirurgie held a very well attended meeting in Munich. Further highlights followed in 1972 with the centenary meeting, and the hundredth congress of the Society held in 1983 in Berlin.

For forty years only a handful of East German colleagues had rare opportunities to participate in the annual congresses that took place mostly in Munich. The first congress after the fall of the Wall was held in Berlin in April 1990 with an overwhelming attendance of surgeons from the East

An official convention building was planned back in the 1870s, modelled on the Royal College of Surgeons of England. The main impetus came from the Empress Kaiserin Augusta who had already supported a number of other humanitarian ventures. In 1915 the Langenbecks-Virchow-House with an auditorium of 1000 seats was inaugurated close to the Charité Clinic in Berlin. It survived the Second World War and served for some time as the Parliament (Volkskammer) of the DDR. The central administration of the Society under its Secretary-General, Professor Edgar Ungeheuer, is based in Munich (Elektrastraße 5).

The official Journal of the Society has always been *Langenbecks Archiv für Chirurgie*, which was founded in 1860.

The President (at present Professor Franz Gall, Erlangen) officiates for 1 year and is supported by a council of five members The majority of the membership is made up of general surgeons, but the Society also embraces specialist sections for trauma, paediatric, vascular, plastic and experimental surgery. Each of these sections is represented in the Präsidium of the Society.

May the humanitarian aim of the society, as put into practice by its numerous members and presidents continue to be Goethe's testimonial for the surgeon. 'To work wonders without words'!

**F. Linder**
**M. Trede**

Officers of the Society·
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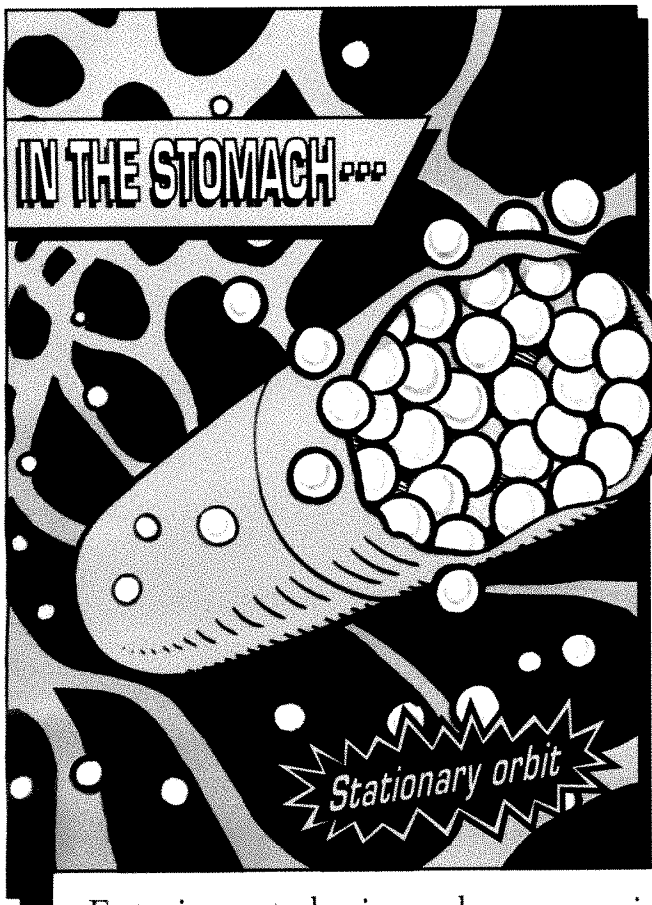

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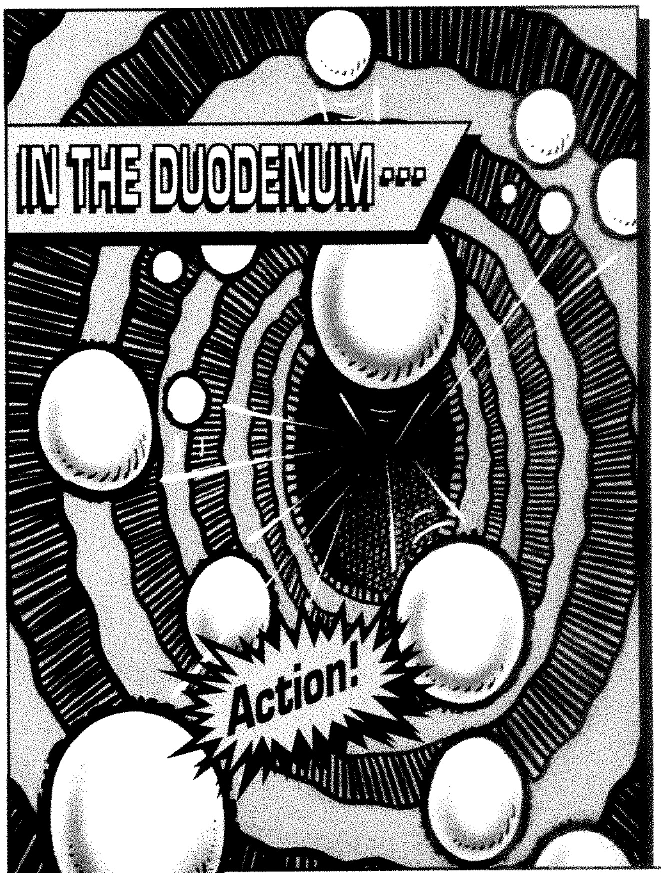
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**References**

1. Stead RJ et al. *Thorax* 1987;**42**:533-537. 2. Beverley DW et al. *Arch Dis Child* 1987;**62**:564-568.

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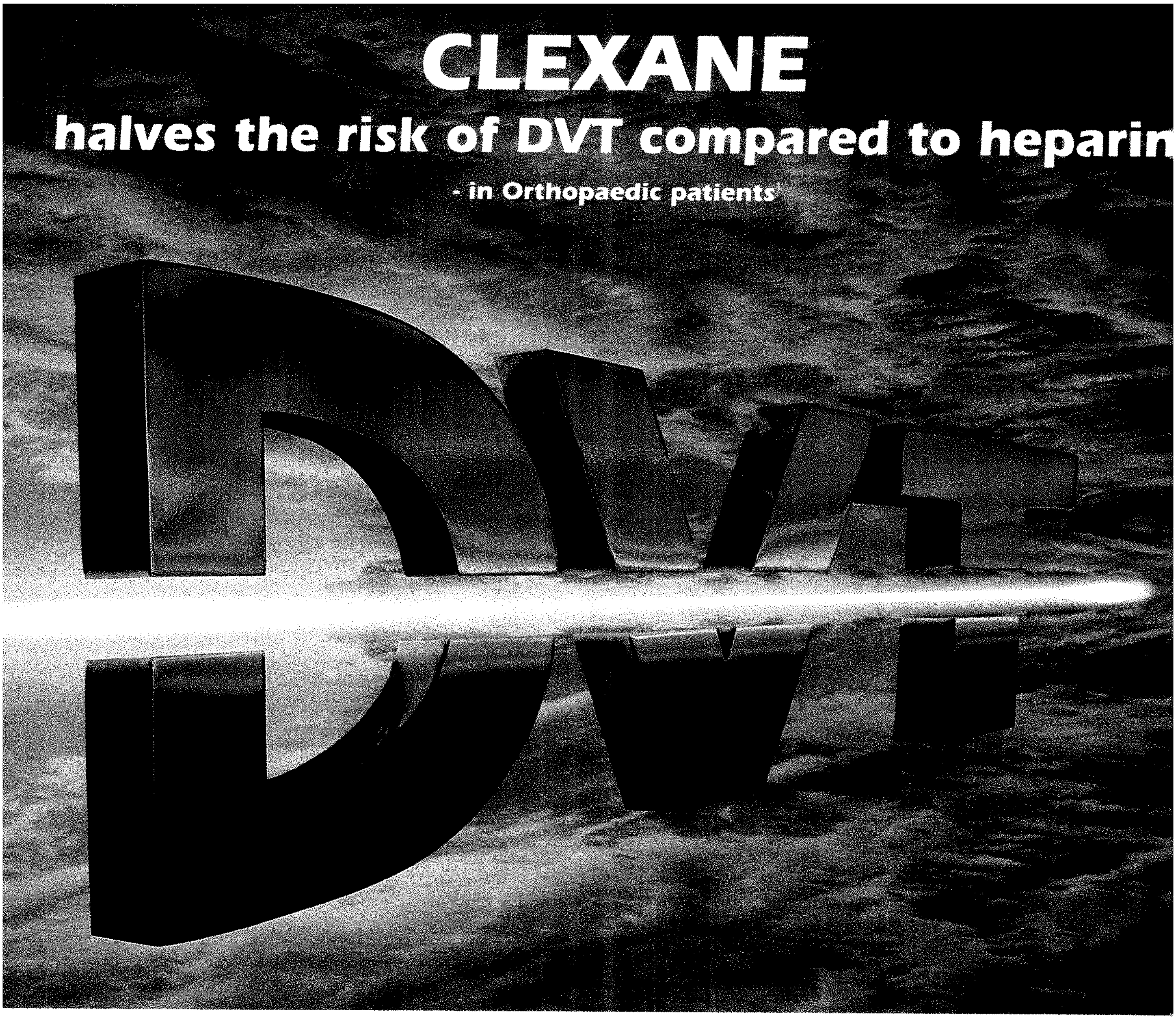
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1. Planes A *et al.* Thrombosis and Haemostasis 1988; **60** (3): 407-410.

Br. J. Surg. 1992, Vol. 79, February, 97–98

# Vein graft surveillance – all part of the service

There is convincing evidence that autologous vein grafts are prone to develop intrinsic faults which threaten failure during the first couple of years after operation. In 1973 Szilagyi identified fibrous strictures in nearly 30 per cent of femoropopliteal saphenous vein grafts during this period[1]. He anticipated that such strictures might be an important cause of graft failure and advocated an aggressive policy of prophylactic surgical intervention. Conventional angiography was the only effective means of detecting strictures at this time and confirmation of their importance was delayed until the advent of digital subtraction angiography (DSA) and duplex ultrasonography, which permitted repeated detailed graft surveillance with safety. Such techniques have now shown that fibrous strictures develop in 20–30 per cent of all vein grafts during the first 12 months after operation[2,3], that these strictures are associated with a threefold risk of graft occlusion, and that they account for up to 80 per cent of all failures occurring during the first 5 years after operation[3]. Furthermore, there are indications that durable long-term improvement in patency rates of between 10 and 15 per cent may be achieved by implementation of a systematic programme of graft surveillance and selective secondary intervention[4].

A number of options exist for the detection of graft stenoses and the choice for the individual surgeon is determined by the resources available to him. Whatever method is used, it is important to ensure that it is capable of achieving the desired result. Angiography remains the gold standard against which all other methods are compared, but standard conventional techniques are not suitable for repeated surveillance of grafts in asymptomatic patients. DSA permits adequate imaging from an intravenous injection of contrast medium and is, therefore, a more suitable test for screening purposes, comparing well in performance with other methods[4,5]. Nevertheless, asymmetrical lesions may be missed unless images are obtained in more than one plane, the test is relatively time-consuming and expensive, and it is not without some discomfort to the patient. Its usefulness can also be compromised in those with a low cardiac output and an effective alternative under these circumstances is intra-arterial DSA employing a low volume of contrast agent injected through a fine bore needle into the common femoral artery.

Duplex scanning provides a real-time B-mode ultrasonographic image of the graft, together with an analysis of Doppler blood flow waveforms; it is an exceptionally powerful tool for the detection of graft stenoses. Accelerated velocity of flow through a stenosis may be utilized to localize such lesions and to assess their severity[5]. Calculation of the peak systolic velocity ratio, from recordings made at the stenosis and at a non-stenosed site in the graft, provides an accurate estimate of the degree of reduction in cross-sectional area. The addition of a colour coding facility to the duplex scanner, while expensive, simplifies the examination and places the test well within the competence of a technician or vascular nurse.

Duplex scanning appears to be extremely accurate for diagnosing stenoses within the main body of a graft or close to the proximal anastomosis, but problems may be encountered in assessing the distal anastomosis and run-off vessels. An alternative technique is to compute the input impedance of the graft and run-off vessels from non-invasive measurements of instantaneous blood flow velocity and pressure[6]. A high level of impedance indicates that the graft is under threat and warrants further assessment by angiography.

DSA, duplex scanning and impedance analysis all require sophisticated and expensive equipment, and a fairly high level of technical expertise which may not be available in all hospitals where vascular surgery is practised. What is needed is a simple, inexpensive, universally applicable test, but unfortunately this continues to be an elusive goal. Nearly all graft stenoses are asymptomatic until the moment of thrombosis. Also, there is usually a paucity of clinical signs, although occasionally a localized bruit may be present. Resting ankle artery Doppler pressure measurements are usually unhelpful. While Doppler measurement after exercise may provide more reliable evidence of graft stenosis, there is considerable controversy about the effectiveness of such a test in practice. If a fall after exercise in ankle:brachial pressure index of $>0{\cdot}2$ is taken as the criterion of a positive result, only 10–15 per cent of strictures are detected[4,5]. However, by accepting a reduction in index of only 0·1, 75 per cent of grafts shown to have a stenosis by duplex scanning may be identified[7]. The problem is that a change of 0·1 is close to the measurement error

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of the test. This means there is likely to be a large number of false positives as well as false negatives, and a large number of people may therefore have unnecessary angiograms. It is questionable whether a surveillance programme based on this method is likely to be any better than no surveillance at all.

Most prospective studies show that the majority of graft stenoses occur within the first 6 months after implantation. The most dangerous lesions develop very soon after operation and progress rapidly, so screening should be most intensive during the first few weeks after operation and become less frequent with time. The yield of new strictures after 9 months does not justify continuing surveillance beyond this time. A practical and effective surveillance programme should include an examination immediately before discharge from hospital, and then at 4 to 6 weeks, 3 months, 6 months and 9 months after operation. A programme such as this may be expected to identify over 95 per cent of all strictures[2–5].

There are two principal options available for treating vein graft stenoses: balloon angioplasty and revisional surgery. Balloon angioplasty has the advantage of being relatively quick and simple, but it is effective only for short stenoses[8]. The results with lesions >2 cm long are poor, and such lesions require surgical correction which, for technical reasons, is also more appropriate for stenoses at or close to the proximal anastomosis. Effective surgical techniques include vein patch angioplasty, interposition grafting, or jump grafting to extend a bypass to a more distal site[8]. Since not all graft stenoses lead inevitably to occlusion, a selective policy of secondary intervention is appropriate. Based on all available information, the following criteria are recommended for elective secondary intervention: (1) recurrence of ischaemic symptoms; (2) reduction of the cross-sectional area of the graft by more than 70 per cent as determined by duplex-derived peak systolic velocity ratio (equivalent to a 50 per cent diameter stenosis); (3) fall in ankle:brachial pressure index of >0·2 after exercise; (4) evidence of progression of stenosis on repeated examinations; and (5) stenosis first detected within 6 weeks of operation.

The principal justification for surveillance programmes is the maintenance of patency of a number of grafts which would otherwise fail, but in these increasingly cost-conscious days this alone is not always sufficient. It is necessary also to demonstrate that they are cost-effective. Factors such as the frequency of screening and the expected yield of positive results are important in this regard. For the programme outlined above, using a monochrome duplex scanner and assuming a turnover of about 100 grafts per year, the total annual cost, including the elective repair of 20 vein graft stenoses, is approximately £50 000[9]. Since each major lower limb amputation costs over £25 000, it is apparent that limb loss has to be prevented in only 2 per cent of patients for the programme to be cost-effective.

If the purchaser of a new motor car can expect guaranteed after-sales service targeted against possible early mechanical breakdown, surely the recipient of a vein graft has the right to expect after-care which is at least as attentive and effective in averting disaster. Until the problem of fibrous stenoses has been eliminated altogether, vein graft surveillance should be an integral component of every vascular surgical service.

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# Acute colonic pseudo-obstruction

*The syndrome of acute colonic pseudo-obstruction is well delineated but its aetiology remains poorly understood and patients are still treated inappropriately. This article reviews the pathogenesis and surgical management of this condition. Early diagnosis is stressed as a pivotal factor in reducing morbidity and mortality.*

Acute colonic pseudo-obstruction (ACPO) is a clinical condition with the symptoms, signs and radiological appearances of acute large bowel obstruction, but without any apparent mechanical cause.

A similar condition was first reported by Murphy in 1896, who described a contracted segment of ileum which spontaneously relaxed during operation in a patient with recurrent lead colic[1]. He called this spastic ileus. By 1930, Zimmerman had reviewed 159 cases of spastic ileus ascribed to a variety of local and distant causes[2]. In 1948 Ogilvie identified a cause of this functional obstruction in two patients with malignant infiltration of the coeliac plexus[3]. Both patients presented with such convincing features of acute distal large bowel obstruction that, despite a normal barium enema, a laparotomy was performed.

The term intestinal pseudo-obstruction was introduced by Dudley and colleagues in Edinburgh a decade later[4] to describe 13 patients in whom a diagnosis of mechanical intestinal obstruction was not substantiated at laparotomy. Since then, the term Ogilvie's syndrome has been used synonymously with ACPO and numerous reports have appeared describing patients with this condition[5–29].

Despite the accurate description of this syndrome, diagnosis is often delayed and many patients are still inappropriately managed, which in turn results in an increase in morbidity and mortality[30]. We have reviewed the aetiology, clinical features and current concepts of the management of ACPO and propose a system for the management of these patients. The problems of chronic pseudo-obstruction of the colon or the rare group of patients with recurrent acute large bowel distension are not discussed.

## Pathogenesis

The first classification founded on aetiology was proposed by Dudley *et al.*[4]. The pathogenesis of the syndrome is unknown, but in more than 80 per cent of cases ACPO appears to be a complication of other clinical conditions[13–19,22,24–29]: in few patients does the pseudo-obstruction occur in isolation and is therefore truly idiopathic[24–29]. *Table 1* lists the many conditions that have been associated with ACPO.

The largest group of clinical conditions that have been linked to ACPO follows normal pregnancy, caesarean section or pelvic surgery and trauma[14,15,18,22,28]. Munroe and Jones have suggested that after spontaneous delivery or caesarean section the uterus may fall back into the pelvis and cause a mechanical obstruction in the distal sigmoid colon[51], others that pelvic surgery, retroperitoneal tumour or haemorrhage may lead to a dysfunction of the sacral parasympathetic nerves (S2, S3, S4) supplying the left colon and rectum, rendering the bowel atonic or spastic and causing a functional obstruction[15,18]. This is plausible, as the transition between dilated and collapsed bowel is often at or near the splenic flexure[28,52] and it is at this point that the parasympathetic innervation of the colon changes from the vagus to the sacral nerves[15].

The role of the autonomic nervous system in modulating colonic activity is still not fully understood. It is thought to act in a facilitatory role; the sympathetic nerves are inhibitory and the parasympathetic nerves are excitatory[53]. An interaction between these systems results in the mechanical activity of the colon; mechanoreceptors have been identified within the colonic wall in animals[54], as has a reflex arc involving colonic afferent pathways and efferent nerves from the sympathetic prevertebral ganglia[55]. Colonic distension stimulates the mechanoreceptors and activates this reflex, resulting in inhibition of motor activity in the large bowel[55]. Such a colocolonic reflex has been postulated in the human colon[53], which would account for progressive colonic distension once the afferent limb of the pathway is activated.

An imbalance in the autonomic innervation of the colon was originally suggested by Ogilvie[3], who postulated that malignant subdiaphragmatic infiltration interrupted the sympathetic supply of the colon leaving unopposed parasympathetic action. This would produce a regional contraction in the colon leading to a functional obstruction. More recently it has been proposed that reflex sympathetic stimulation producing intestinal inhibition may be an important factor in the evolution of ACPO[24,56]. This would seem logical because patients with acute pseudo-obstruction are often ill[30] and therefore have an increased intrinsic sympathetic drive[12]. An increase in sympathetic activity in the colon causes dilatation of the large bowel[15] which may be the precursor of acute pseudo-obstruction. Neely and Catchpole have shown that the myogenic contractility of the gut is unimpaired in paralytic ileus and that bowel distension occurs as a result of reflex sympathetic-induced inhibition[57].

The abnormalities of colonic motility which have been implicated in the pathophysiology of ACPO have also been attributed to the associated metabolic disturbances which may lead to disordered neuromuscular transmission[49]. However, histology of the colon of patients with pseudo-obstruction appears normal[58,59]. Elevated circulating levels of prostaglandins E and F have been recorded in a patient with ACPO[60]: while it is known that E series prostaglandins can cause relaxation of human intestinal circular smooth muscle[60], their precise role in the genesis of pseudo-obstruction is not clear.

There remains a group of patients in whom no specific underlying disorder can be identified[24–29]. Thus the exact pathogenesis of pseudo-obstruction remains unknown, perhaps because several mechanisms may be involved. However, colonic

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**Table 1** *Conditions associated with acute colonic pseudo-obstruction*

- Idiopathic[4,5,8,9,11,12,15,16,21–25,27]
- Cardiovascular
  - Myocardial infarction[10,14,15,17,26,28]
  - Congestive cardiac failure[10,12,24]
  - Cerebrovascular accident[12,25,31]
  - Subarachnoid haemorrhage[25]
  - Pulmonary embolus[14]
  - Mesenteric ischaemia[11]
  - Peripheral vascular disease[7]
- After trauma
  - Intra-abdominal[18,19,32,33]
  - Pelvic fractures[14,15,18]
  - Spinal fractures/retroperitoneal haematoma[18–20,25,27]
  - Femoral fractures[14,16,20,26,27,32]
  - Burn injury[34]
- After operation
  - Abdominal surgery[17,18,35]
  - Pelvic/gynaecological surgery[7,15,18,22,27,36–39]
  - Postpartum[28,40,41]
  - Caesarean section[7,14,15,18,42]
  - Renal transplantation[26]
  - Cardiothoracic surgery[17,43]
  - Hip surgery[14,18,19,24–26]
  - Spinal surgery[21,25]
  - Neurosurgery[11,13]
- Malignant
  - Retroperitoneal[3]
  - Disseminated[26]
  - Leukaemia[16,24]
  - Pelvic radiotherapy[29,44]
  - Phenol ablation of renal tumour[45]
- Infective/inflammatory
  - Intra-abdominal/pelvic abscess[7]
  - Acute appendicitis[11]
  - Acute cholecystitis[10,12,24,28]
  - Acute pancreatitis[14]
  - Systemic sepsis[7,19,21,24,29]
  - Herpes zoster infection[46]
- Respiratory
  - Pneumonia[7,12,14,15,17,19,24,27]
  - Mechanical ventilation[28,47]
- Metabolic
  - Electrolyte disturbances[11,15,20,29,48]
  - Renal failure[4,8,24,26,29]
  - Liver failure[27]
  - Alcohol abuse[11,13,49]
  - Thyroid dysfunction[25]
  - Diabetes[25,26]
  - Parkinson's disease[16,18]
- Drugs
  - Antidepressants[25]
  - Phenothiazines[20,25]
  - Antiparkinsonian[25]
  - Opiates/narcotic addiction[26,29]
- Neurological
  - Nerve root compression[16]
  - Multiple sclerosis[11,19]
  - Low spinal cord disease[50]

dysmotility is probably the final common pathway, although it may be produced by a variety of physiological and biochemical disturbances.

## Clinical features

The clinical features of this syndrome closely mimic acute large bowel obstruction[30,39]. The clinical setting is often helpful in making the diagnosis; patients are often already in hospital, have a concomitant systemic illness, are postpartum or recovering from surgery or pelvic or spinal injury[30].

Colicky abdominal pain is a frequent complaint[28] and the abdomen progressively distends[30]. Constipation is common[28], though often not absolute as some patients continue to pass small amounts of flatus or liquid stool[14,30,58]. Nausea and vomiting are also common[28]. Fever may occur at any time, but is more frequent in patients with ischaemic or perforated bowel[28].

The most dramatic physical finding is massive abdominal distension[14,25,28]. Abdominal tenderness is often less than expected[14,25,28] but its presence, particularly in the right iliac fossa, may indicate incipient perforation of the caecum[13,22,61,62]. The quality of the bowel sounds is variable and can be normal, reduced or even obstructive in nature, but sounds are rarely absent[13–15,22,35]. Digital examination usually reveals an empty rectum.

## Investigations

Laboratory investigations are not diagnostic but uraemia or electrolyte disturbances may suggest a cause for the pseudo-obstruction. A leucocytosis may occur, especially in the presence of perforated or ischaemic bowel[14,17,35,42,58,63].

Plain abdominal radiography is the most useful investigation[11,14,16,25] and may show distal colonic obstruction (*Figure 1*) with dilatation of the proximal large bowel[11,14,16,25,58,64]. ACPO should be distinguished from a volvulus of the caecum or sigmoid colon[64]. Distended loops of small bowel are seldom seen[11,18,64]. The dilated colon is predominantly gas-filled, with little fluid, making the appearance radiologically of air–fluid levels uncommon[14,42,58,64]. Unlike mechanical large bowel obstruction, the colonic haustral and mucosal pattern is maintained[27,58,63–65] and distinguishes it from the toxic megacolon of inflammatory bowel disease[65].

The gas pattern of the distended colon has a clear cut-off, most commonly at the splenic flexure but also at the rectosigmoid junction and hepatic flexure[28]. These areas represent junctions where the mobile colon becomes fixed and it has been suggested that colonic distension proximal to these points may cause a kink in the bowel, producing mechanical obstruction[66].

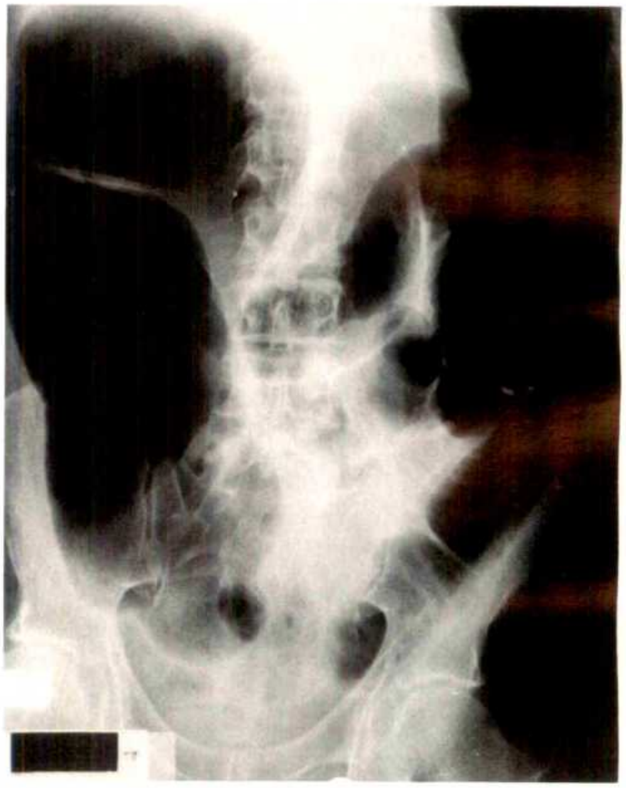


**Figure 1** *Plain abdominal radiograph of a patient with acute colonic pseudo-obstruction showing massive caecal distension and a clear gas cut-off at the rectosigmoid area*

A pneumoperitoneum may be visible on an appropriate radiograph if perforation has occurred; however, a pinhole perforation that is rapidly sealed may produce insufficient gas to be detected radiographically[28]. Perforation most commonly occurs in the caecum as a result of progressive colonic distension, which causes local ischaemia and longitudinal splitting of the serosa and herniation of the mucosa[28,64]. Further distension leads to disruption of the mucosa. In general, the caecal diameter is larger in patients with perforation or ischaemic bowel[28]. Perforation is unlikely when the caecal diameter is less than 12 cm; the risk increases significantly with measurements of 14 cm or more[33,43,56,61–63,67–74]. The measurement of caecal diameter on sequential abdominal radiographs is therefore of considerable use in the management of these patients.

## Management

### *Diagnosis*

Because the treatment of patients with mechanical colonic obstruction is different from those with ACPO and because ACPO may coexist with a previously asymptomatic carcinoma of the colon, a firm diagnosis is essential to avoid inappropriate and dangerous measures being taken[17,30,39]. The clinical picture may suggest malignant colonic obstruction but differentiation from pseudo-obstruction can be difficult, particularly in patients with idiopathic ACPO[39]. Large bowel obstruction requires urgent surgical intervention only when the patient already displays localizing signs of peritoneal irritation: there is no place for an undirected diagnostic laparotomy in the absence of such signs, as patients with ACPO often fare badly after laparotomy because of an underlying illness[30]. There will usually be time to establish the diagnosis by one of two methods – contrast enema[64,75,76] or colonoscopy[59,77].

The value of contrast enema in the management of patients with colonic obstruction is undisputed[64,75,76]. It can confirm the diagnosis of functional obstruction or reveal the site of a mechanical obstruction and should be preceded by rigid sigmoidoscopy to exclude a high rectal carcinoma. Dilute barium sulphate and water-soluble contrast media have both been used[64,75,76], but enemas are contraindicated if the patient displays peritoneal irritation[64]. The osmotic effect of a water-soluble medium is often therapeutic in decompressing the colon[34,75,76]. Furthermore, its use obviates the risk of peritoneal contamination with barium should there be a perforation or should laparotomy be necessary[76]. If the barium enema is equivocal then colonoscopy should be performed.

Emergency colonoscopy has been described as a method of diagnosis and treatment in patients with ACPO[59,77], but in this situation colonoscopy can be difficult, hazardous and requires considerable experience and skill[59,77]. In addition, colonoscopy is less likely to be available than contrast radiology and a cautious contrast enema is simpler and safer to perform[30].

### *Conservative treatment*

Once the diagnosis has been confirmed management is essentially conservative, including nasogastric decompression, minimal oral intake, correction of fluid and electrolyte abnormalities and treatment of any associated conditions or infections[14,18,22,35,58,59,64]. Withdrawal of any opiate or anticholinergic drugs is also important[28]. The cautious passage of a flatus tube may help decompress the colon when the distension extends distally[10,35], but enemas or rigid sigmoidoscopy are seldom effective[31,58,63].

Neely and Catchpole's regimen of combined pharmacological sympathetic blockade and parasympathetic stimulation[78] to treat postoperative ileus may also be of value in decompressing the colon[25,76,77], but stimulation is contraindicated when the caecum is grossly distended[77]. The motility-enhancing drug cisapride has been used with some success in patients with ACPO[79,80]. Studies have shown that cisapride induces colonic contraction and shortens colonic transit time[81,82]. Current evidence indicates that it acts by enhancing the release of acetylcholine in the myenteric plexus of the gut wall[83]. Epidural anaesthesia, which produces sympathetic blockade, may also be effective[84].

It should be emphasized that the colon, although not mechanically obstructed, may nevertheless dilate to the point of caecal rupture[30,33,43,56,61–63,67–74] and so careful and repeated clinical assessment of the patient, preferably by the same observer, is essential. Plain abdominal radiography should be performed every 12–24 h to study the caecal diameter[11,21].

Conservative therapy should be continued for 48–72 h provided that there is no right iliac fossa tenderness and the caecum is not grossly distended. If there is a progressive increase in caecal diameter or no improvement is seen with a conservative regimen, the colon should be decompressed without further delay to avoid the risk of caecal ischaemia or perforation[11,14,17,18,21,64]. The development of caecal tenderness is an absolute indication for laparotomy[21,22,61].

### *Colonoscopy*

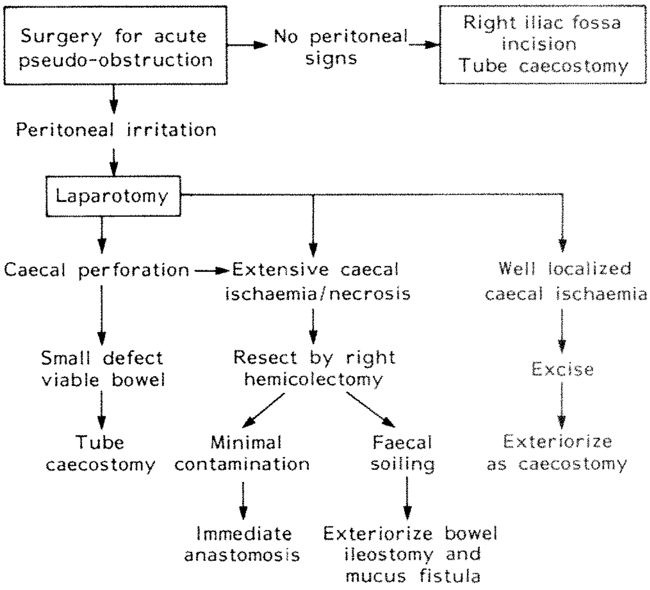
Successful colonoscopic decompression for ACPO was first described by Kukora and Dent in 1977[85] and its use is now established in the management of ACPO[18,34,59,77,86–89]. However, unprepared bowel containing copious amounts of thick, viscid stool makes the procedure difficult and potentially dangerous. Repeated gentle saline enemas before colonoscopy significantly improve visibility[59,85]. Air insufflation should be kept to a minimum to prevent any further increase in pressure within the caecum. In this situation colonoscopy is time-consuming, taking an accomplished operator 45–60 min[59]. This form of treatment is associated with a mortality rate of between 2 and 5 per cent[59,85].

It is not necessary to pass the colonoscope to the caecum, as adequate decompression can be achieved if the hepatic flexure is reached[59,84]. If colonoscopy reveals evidence of colonic ischaemia (blood-stained fluid or haemorrhagic friable mucosa), the procedure should be abandoned and laparotomy performed[44,59,86]. Successful decompression may be expected in approximately 80 per cent of patients after the initial colonoscopy[59,84]. Recurrence occurs in up to 15 per cent of cases[59,85], and in these patients the procedure may be repeated. However, if the distension remains refractory, caecostomy should be performed without further delay[59,84]. Recently colonoscopy has been refined to allow vented tubes to be positioned in the caecum with the aid of the colonoscope[90–93], which enables a transanal tube to be left in the caecum to prevent or treat recurrent distension.

### *Surgery*

The indications for surgery for ACPO are failure of conservative treatment and colonoscopy, or clinical signs indicating impending or actual caecal perforation[28,59,64]. The surgical management of ACPO is summarized in *Figure 2*.

In the absence of ischaemic or perforated bowel, tube caecostomy is the procedure of choice as successful decompression is the rule and the complications few[10,11,14,17,18,24]. This can be performed through a limited right iliac fossa incision to expose the caecum, if necessary using local anaesthesia[10,14,17,24]. A large Foley catheter should be used to intubate the caecum. The tube may be removed after 2 or 3 weeks and the stoma should contract and close spontaneously[24,39]. There is considerable debate as to the use



Surgery for acute pseudo-obstruction
No peritoneal signs
Right iliac fossa incision
Tube caecostomy
Peritoneal irritation
Laparotomy
Caecal perforation
Extensive caecal ischaemia/necrosis
Well localized caecal ischaemia
Small defect viable bowel
Resect by right hemicolectomy
Excise
Tube caecostomy
Minimal contamination
Faecal soiling
Exteriorize as caecostomy
Immediate anastomosis
Exteriorize bowel ileostomy and mucus fistula

**Figure 2** *The surgical management of acute colonic pseudo-obstruction*

of tube caecostomy rather than formal caecostomy[14,30]. Dudley and Paterson-Brown[30] have emphasized the hazards of tube caecostomy; moreover, the formation of a formal caecostomy obviates the potential complication of a blocked catheter. However, decompressive transverse colostomies and diverting ileostomies produce uniformly unsatisfactory results[10,24,28] and carry a mortality rate of up to 40 per cent compared with 15 per cent for tube caecostomy[28].

If the clinical signs suggest caecal ischaemia or perforation then laparotomy should be performed through a vertical incision[39] (*Figure 2*). The choice of procedure is dictated by the state of the caecum: if there is extensive necrosis of the caecum, it should be resected[14,18,64]; an immediate anastomosis should be deferred if there is widespread faecal contamination, in which case an ileostomy and a mucus fistula should be performed[17,61]. The remaining large bowel, particularly the ascending and transverse colon, should be inspected carefully to exclude other areas of ischaemic necrosis or perforation[61]. On a cautionary note, however, we have had personal experience of two patients in whom ACPO developed in the residual colon following right hemicolectomy. In the presence of a well localized area of caecal ischaemia, the area should be excised and exteriorized as a formal caecostomy[14,33]. In cases of caecal perforation, if the surrounding bowel is viable and the defect small with minimal faecal spillage, the perforation may be either exteriorized[14,18,28] or intubated[17,28,61,62]; otherwise, the caecum should be resected by right hemicolectomy[14,18,61].

## Outcome

With appropriate management the pseudo-obstruction usually resolves in 3–6 days[28]. However, there is a significant mortality rate even when adequate colonic decompression is achieved, as patients are often debilitated[64,85]. Many in-hospital deaths are due to underlying illness and are unrelated to the syndrome or its treatment[28]. The mortality rate for patients undergoing surgery is 30 per cent compared with 14 per cent in those treated conservatively[28]; it is noteworthy that tube caecostomy alone and conservative management carry similar mortality rates[28].

The age of the patient, the presence of an ischaemic or perforated caecum and delay in colonic decompression significantly affect outcome[28]. The reported incidence of caecal perforation varies between 14 and 40 per cent[22,28,61], and in its presence the mortality rate increases to 40 or 50 per cent[28,61,72]. Thus, apart from the age of the patient, all other high-risk factors are potentially controllable.

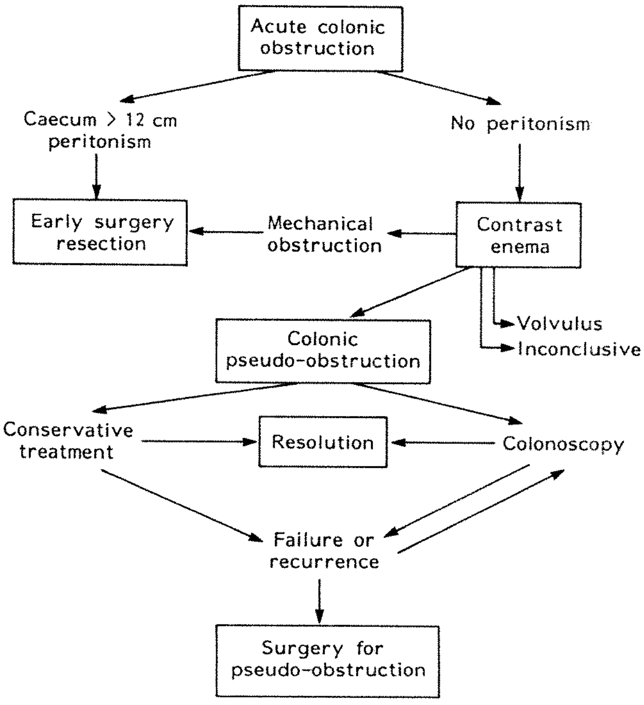


**Figure 3** *Algorithm for the management of acute large bowel obstruction*

It is suggested that patients with clinical acute large bowel obstruction in whom the caecum is not threatened should undergo a limited contrast enema examination that will enable prompt diagnosis of ACPO and prevent unnecessary and hazardous surgery. A clinical algorithm is proposed for the management of such patients (*Figure 3*).

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# Anal endosonographic findings in the follow-up of primarily sutured sphincteric ruptures

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*Twenty-four women with primary suture of an obstetric tear of the anal sphincter were examined with anal endosonography a median of 12 (range 3–18) months after delivery. Endosonography was normal in ten patients, of whom one was incontinent. The examination showed a defect in the external anal sphincter in 13 patients; six of these were incontinent, two of whom had normal findings on palpation. An isolated internal sphincter defect was found in a continent patient. Since anal endosonography causes no more discomfort than digital examination, it may be useful to identify patients who would benefit from surgical reconstruction of the anal sphincter.*

Obstetric tears and rupture of the anal sphincters may result in anal incontinence despite primary repair. Anal manometry is used to evaluate the function of the anal sphincter, but its results may be poorly correlated to the presence or absence of anal incontinence in these patients[1]. If manometry shows low values after childbirth, restoration to normal values should indicate that recovery of the anal sphincter is complete, but this is not always the case[1,2].

The internal and external anal sphincters can be visualized with anal endosonography[3,4], which has been used to demonstrate sphincteric defects in incontinent patients[5,6]. The aim of this study was to determine whether anal endosonography could visualize any sphincteric abnormalities in patients after primary repair of anal sphincter rupture and to identify by means of anal endosonography patients who might benefit from surgical reconstruction of the anal sphincter.

## Patients and methods

Twenty-four women, median age 30 (range 24–38) years who had undergone primary suture of an obstetric tear of the anal sphincter entered the study after giving informed consent. All sutured defects had healed without complication.

Anal manometry and anal sponge electromyography (EMG) were performed within 1 week after delivery, after 3 months, and in some cases after 6 and 12 months. Maximum resting pressure and maximum squeeze pressure were measured with a perfused low-compliance open-ended polyvinyl catheter connected to a strain gauge (Statham, Bristol, UK) and displayed on a chart recorder (Dantec, Bristol, UK). EMG was performed using a disposable sponge electrode placed in the anal canal and connected to an EMG apparatus (Neuromatic 2000; Dantec). The details of these techniques have been described elsewhere[7,8].

Concentric needle EMG mapping was performed in five patients, always before endosonography. EMG mapping was not performed in all patients as most of them had no anorectal complaints and sphincteric defects were not suspected.

Anal endosonography was performed after a median of 12 (range 3–18) months by the same investigator in all patients. Before the ultrasonographic examination a digital rectal examination to locate any palpable defects was performed by another investigator, who also noted the site of the external scar in the perineum. The ultrasonographic examinations were performed blindly without any knowledge of the clinical findings (grade of incontinence, anal manometry, EMG and findings on digital examination).

Ultrasonographic examinations were performed with the patient in the left lateral decubitus position and without any bowel preparation. Each patient was examined with two different ultrasonographic probes. A Brüel and Kjær (Nærum, Denmark) ultrasonographic scanner was used, type 1846 with a 7 MHz rotating endoprobe type 1850 (focus 2–5 cm, diameter 1·7 cm) covered by a hard sonolucent plastic cone (Brüel and Kjær type WA 0453) filled with degassed water. Axial images were obtained while the probe was slowly withdrawn. In addition, all patients were examined with a Brüel and Kjær 7 MHz multiplanar endoprobe type 8551 (focus 1–6 cm, sector 112°, diameter 2·3 cm). With this probe, each quadrant was examined separately in transverse images. Longitudinal images were obtained by rotating the probe[4].

Results were analysed using the Mann–Whitney $U$ test.

## Results

Anal endosonography shows the internal sphincter as a 2–3 mm thick circular hypoechoic band[3,4]. The external sphincter is a broader and more echogenic band, located just outside the internal sphincter (*Figure 1*).

Endosonography was normal in ten patients. In one patient an isolated internal sphincter defect was found. In 13 patients a hypoechoic defect could be identified within the echogenic external sphincter (*Figure 2*). All defects were found in one of the anterior quadrants, and in all patients the defect corresponded to the site of the external scar on the perineum. Five of these patients underwent concentric needle EMG, which confirmed the external sphincter defects seen by endosonography. One patient underwent surgical reconstruction of the anal sphincter, which confirmed the external sphincter defect.

In seven of 13 patients in whom endosonography revealed a defect, this could be felt by digital examination. Digital examination was normal in the remaining patients.

Seven patients had persisting incontinence. In six of these

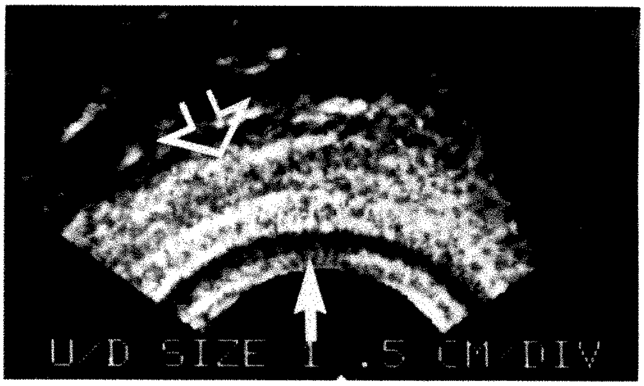

**Figure 1** *Transverse section of the anal canal with the multiplane transducer showing the normal endosonographic appearance of the hypoechoic (dark) internal sphincter (solid arrow) and the external sphincter, which is the broad echogenic (bright) band just outside the internal sphincter. The open arrow indicates the outer limit of the external sphincter*

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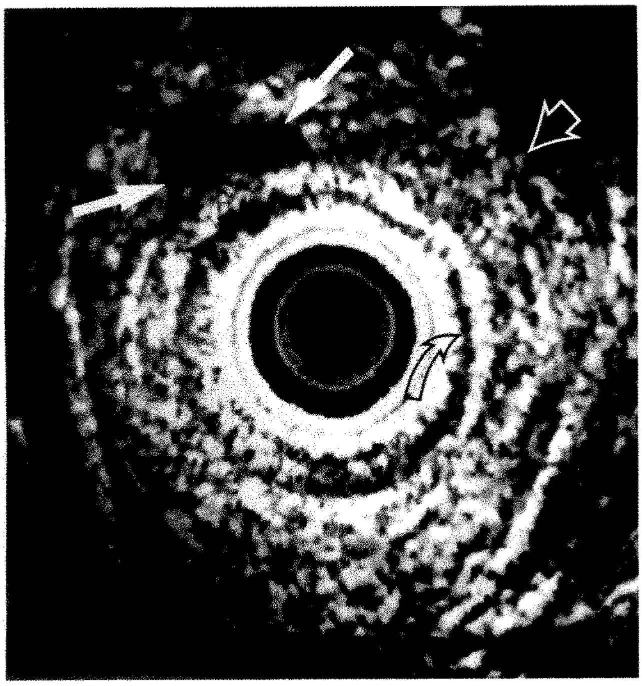

**Figure 2** *Transverse section of the anal canal with the rotating endoprobe, seen from below with the anterior quadrants at the top. A dark defect (solid white arrows) is seen within the bright external sphincter at the 10–11 o'clock position in an incontinent patient. The internal sphincter is the circular hypoechoic band (curved arrow). The external sphincter is the circular echogenic band (the open white arrow indicates the outer limit)*

a hypoechoic defect within the external sphincter was found by endosonography (*Table 1*), and in four of these patients a defect was found on digital examination. Some patients had decreased anal pressure and EMG amplitude, but no correlation with the degree of anal incontinence was demonstrated.

The internal sphincter defect and the remaining seven external sphincter defects were found in fully continent women with normal manometric findings and normal anal sponge EMG.

A comparison between the ten women who had normal endosonography and the 13 women who had external sphincter defects showed no significant difference in manometry or anal sponge EMG measured 1 week after delivery (*Table 2*). The anal physiology parameters measured 3 months after delivery tended to be lower in the group with external sphincter defects (*Table 2*), but no significant difference was found ($P > 0{\cdot}05$).

In 14 patients, manometry and anal sponge EMG were performed after 6 months, and in six of them also after 12 months, but these values did not differ from those obtained at 3 months.

## Discussion

Anal endosonography demonstrated hypoechoic areas within the echogenic external sphincter in 13 patients. These areas could be visualized with both types of endoprobe and were located at the site of the previous sphincteric rupture. These hypoechoic areas probably represent defects in the sphincter, and supporting evidence for this was found by needle EMG in five patients.

Anal endosonography has been used to detect sphincteric defects in incontinent patients[5,6], but it has never been used in

**Table 1** *Findings on investigation in patients with persisting incontinence after primary suture of an obstetric tear of the external sphincter muscle compared with nine continent patients*

| | | | | Maximal anal pressure | | Anal sponge electromyography | |
|---|---|---|---|---|---|---|---|
| Age (years) | Endosonographic findings | Findings on digital examination | Incontinence | Rest ($cmH_2O$) | Squeeze ($cmH_2O$) | Rest ($\mu V$) | Squeeze ($\mu V$) |
| 30 | Normal | Normal | Flatus | 120 | 160 | 24 | 184 |
| 24 | External sphincter defect | Defect | Liquid stool | 26 | 60 | 20 | 145 |
| 24 | External sphincter defect | Defect | Solid stool | 50 | 120 | 40 | 288 |
| 29 | External sphincter defect | Defect | Flatus | 55 | 70 | 22 | 53 |
| 35 | External sphincter defect | Defect | Flatus | 25 | 70 | 124 | 460 |
| 31 | External sphincter defect | Normal | Flatus | 80 | 110 | 32 | 148 |
| 29 | External sphincter defect | Normal | Liquid stool | 45 | 90 | 148 | 268 |
| | Normal ($n = 9$) | Normal | Continent | 63 (40–95) | 105 (55–205) | 74 (22–148) | 272 (55–344) |

Values for continent patients are median (range)

**Table 2** *Endosonographic results at median 12 (range 3–18) months after delivery in women with primary suture of obstetric tears compared with anal physiological examinations 1 week and 3 months after delivery*

| | | | | Maximal anal pressure | | Anal sponge electromyography | |
|---|---|---|---|---|---|---|---|
| Endosonography | Number of patients | Number of incontinent patients | Anal physiology | Rest ($cmH_2O$) | Squeeze ($cmH_2O$) | Rest ($\mu V$) | Squeeze ($\mu V$) |
| Normal | 10 | 1 | | | | | |
| | | | 1 week | 50 (30–140) | 68 (45–245) | 31 (7–96) | 101 (13–156) |
| | | | 3 months | 69 (40–120) | 108 (55–205) | 67 (22–148) | 256 (58–344) |
| External sphincter defects | 13 | 6 | | | | | |
| | | | 1 week | 45 (20–90) | 69 (40–105) | 28 (7–124) | 97 (35–224) |
| | | | 3 months | 55 (25–80) | 105 (60–145) | 40 (20–148) | 176 (53–460) |

Values for anal physiology results are median (range) the follow-up of sphincteric ruptures. The presence of endosonographic external sphincteric defects in a high proportion (seven of 17) of fully continent patients after primary suture of obstetric tears has never been reported.

Surgical reconstruction of the external sphincter might be considered in incontinent patients in whom endosonography shows a defect. In this study one patient with an endosonographic defect and incontinence for liquid stool underwent surgical reconstruction of the anal sphincter and a further patient is awaiting operation.

Seven patients in this study were fully continent although endosonography revealed a defect within the external sphincter. This may be due to the fact that the women in this investigation are young, and some are able to compensate for a non-functioning part of the external sphincter muscle by the action of the puborectalis and the pelvic floor muscles. It is likely that, as they grow older, some of these women will lose this ability to compensate and will therefore develop incontinence.

Every patient was examined with two different ultrasonographic probes. The rotating endoprobe has the advantage of giving 360° axial images of the anal canal, making it possible to compare the left and right sides, which should be identical in normal subjects. The multiplane probe examines a sector of only 112°, making it difficult to observe a large defect located close to the probe, as it will fill the whole sector. The sphincteric defects were seen most easily with the rotating endoprobe. Consequently, this probe only is now used to examine these patients.

Only one defect was seen within the internal sphincter, which theoretically could be due to the fact that the internal sphincter is too close to the probe and not in the focal distance. This is, however, not likely, as other studies have shown that internal sphincter defects can be clearly visualized after internal sphincterotomy[3].

In other reports, 48 and 42 per cent of women with obstetric tears of the anal sphincter were incontinent[2,9]. In this report, seven of 24 women (29 per cent) had persisting incontinence. It was not possible, based on the manometry or EMG values, to detect which women would develop persisting incontinence. In four of seven patients the degree of incontinence was relatively mild and this may explain why no correlation between manometry and incontinence was found. Another explanation might be that, although some incontinent women had manometric findings and anal sponge EMG values that were lower than normal, there was a considerable overlap with values found in continent women with normal endosonography.

In our opinion, endosonographic defects of the external sphincter, whether found in continent or in incontinent women, should be considered a risk factor, and these women should be informed of the risk carried by any further anal or perianal trauma. It is possible that in future pregnancies these women should be offered a caesarean section to avoid further damage, although there are no data to support this.

Careful digital examination may reveal some, but not all, of the external sphincter defects. A report has described mapping of external sphincter defects after perineal trauma in both male and female patients using anal endosonography with a rotating endoprobe[5]. In the present study anal endosonography was able to demonstrate defects within the external sphincter in 13 of 24 patients after primary suture of a tear of the anal sphincter. As anal endosonography causes no more discomfort than digital examination and can be completed in 10 min, this technique should be used to identify patients in whom surgical reconstruction of the sphincter at an early stage might be considered.

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# Abdominal rectopexy for rectal prolapse: a comparison of techniques

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*To compare the methods of abdominal rectopexy and to elucidate the mechanism by which rectopexy restores continence in patients with rectal prolapse, the role of sphincter recovery, rectal morphological changes and improved rectal sensation were assessed in 68 patients (eight men, 60 women) of median age 63 (range 18–83) years undergoing resection rectopexy* (n = *29), anterior and posterior Marlex® rectopexy* (n = *20), posterior Ivalon® rectopexy* (n = *9) or suture rectopexy* (n = *10). Preoperative and postoperative manometry, radiology and electrosensitivity measurements were made. Age and duration of follow-up were similar in all groups and the prolapse was controlled in all patients. Significantly improved continence was seen in all but the Ivalon group. There was no evidence of increasing postoperative constipation. Sphincter length and voluntary contraction were unaltered, but improved resting tone was seen in the resection and suture groups. This was not seen in the prosthetic groups. Improved continence correlated with recovery of resting pressure. Upper anal sensation was improved in all groups. Radiological changes did not correlate with improved continence. We conclude that continence is improved by all rectopexy procedures but seems better without prosthetic material. Sphincter recovery seems to be the most important factor.*

Faecal incontinence commonly accompanies complete rectal prolapse. Although abdominal rectopexy corrects the prolapse in the majority of cases, incontinence may persist in a number of patients. In this respect, abdominal procedures are superior to the perineal ones in that impaired continence is more prone to persist after operations like the Altmeier procedure, which involves a perineal rectosigmoidectomy sometimes accompanied by reefing of the pelvic floor muscles[1,2]. Overall, approximately 75 per cent of patients can expect their continence to be improved following abdominal rectopexy. There is debate surrounding the mechanism of this improvement. In a recent report, postoperative constipation affected 47 per cent[3] and it was suggested that this was the mechanism of improved postoperative continence. Another report ascribed restoration of continence to recovery of the internal sphincter with an increase in postoperative anal canal pressures[4].

This study examined anorectal function before and after surgery prospectively in an attempt to elucidate the mechanisms of postoperative continence.

## Patients and methods

In the 3-year period 1986–1989, 68 abdominal rectopexies were carried out by one of the authors (D.C.C.B.) at the Bristol Royal Infirmary (*Table 1*). The male:female ratio was 8:60, with a median age of 63 (range 18–83) years. Using standard physiological history sheets, preoperative and postoperative assessment was carried out by an independent assessor (G.S.D.) to avoid operator bias. Objective preoperative and postoperative physiological variables (anal canal manometry, proctometrography, proctography and electrosensitivity) were measured. Postoperative physiological assessment was carried out at 6 months.

### *Continence*

Continence was assessed on a scale similar to that described by Browning and Parks[5]. Grade 1 is normally continent; grade 2 is normally continent to liquids and solids but incontinent to flatus; grade 3 is incontinent to liquids and flatus but normally continent to solids; and grade 4 patients are incontinent to flatus, liquids and solids. In assessing adequate preoperative and postoperative continence, grades 1 and 2 have been accepted as continent, but grades 3 and 4 are defined as incontinent. We believe this to be a socially acceptable definition.

**Table 1** *General details of patients undergoing rectopexy*

| | *n* | Age (years) | Duration of symptoms (months) | Follow-up (months) |
|---|---|---|---|---|
| Suture rectopexy | 10 | 70 (45–76) | 7·5 (2–38) | 11·5 (6–29) |
| Ivalon rectopexy | 9 | 60 (27–71) | 8 (2–25) | 13 (5–15) |
| Marlex rectopexy | 20 | 62 (45–78) | 6·5 (1–24) | 6 (2–12) |
| Resection rectopexy | 29 | 60 (18–83) | 8 (1–27) | 6 (2–12) |

Values are median (range). There were no significant differences between the groups

### *Manometry*

The closed water-filled microballoon system used by this unit is described elsewhere[6]. A station pull-through technique was used to define sphincter length, and maximum resting and maximum voluntary contraction anal canal pressures. The recorder was calibrated before each use. Preoperative and postoperative values have been paired for analysis.

### *Proctometrography*

A similar catheter was covered by a thin latex balloon and placed in the rectum. This was filled at a constant rate (60 ml/min) with water at 37°C to determine the volume required for first awareness of rectal filling.

### *Anal canal mucosal electrosensitivity*

The threshold sensitivity to an electrical stimulus was measured in the lower, mid and upper anal canal as defined by manometry. A graduated catheter bearing two platinum electrodes 1 cm apart and connected to a pulsed constant current generator[7] was used to determine the sensitivity thresholds by slowly increasing the current delivered until a tapping or prickling sensation was reported by the patient. The mean

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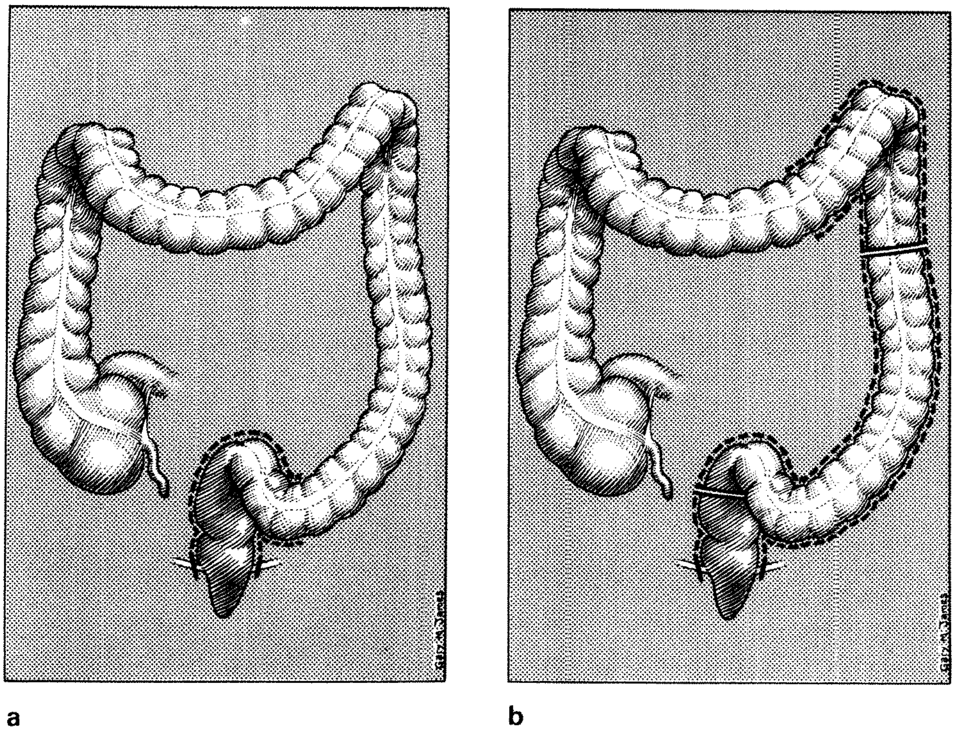

**Figure 1** *Colorectal mobilization for rectopexy:* **a** *for non-resectional procedures (lateral ligaments divided);* **b** *for resection and rectopexy (lateral ligaments divided)*

of three readings was taken as the threshold value at each level in the anal canal. The reliability and reproducibility of this investigation has been confirmed[8].

*Transit studies*

All patients underwent a standard 5-day whole-gut transit study. They were instructed to refrain from the use of stimulant laxatives. Bulking agents were allowed if these were already being used as part of a high-fibre diet. Twenty radio-opaque markers were given on day zero and a plain radiograph of the abdomen was taken on day 5. Patients were considered to have slow transit if >20 per cent of the markers was retained[9].

*Proctography*

Patients were examined in the left lateral position with hips and knees flexed to 90°. The degree of perineal descent and alterations in the anorectal angle were noted with the patients at rest, on maximal contraction of the pelvic floor, and while straining down. Barium and starch paste, simulating rectal contents, was introduced to the previously unprepared rectum while the anal canal was delineated by a radio-opaque ball and chain[10]. The anorectal angle was defined as the angle between a line bisecting the rectum and the line of the anal canal. Perineal descent was assessed from the pubococcygeal line, as the perpendicular distance from this to the anorectal angle. An angle lying below this line was given a negative value for descent. In addition to these static studies, evacuation studies were undertaken with the patient seated on a commode at the same examination and used to confirm complete rectal prolapse.

*Statistics*

All investigative values were expressed as medians with ranges in parentheses. Paired preoperative and postoperative data were assessed by Wilcoxon's paired signed rank test. Correlations were assessed using Spearman's ranked correlation coefficient. $P$ values of $<0{\cdot}05$ were considered as significant for this study. In comparisons between types of treatment, significance was accepted only when confirmed by the Kruskal–Wallis analysis of variance.

*Surgical procedures*

All operations were performed via a transabdominal route. Initially midline incisions were used, but we have now routinely adopted a low transverse muscle-cutting approach. A full mechanical bowel preparation and perioperative antibiotic regimen was used.

*Non-resectional rectopexy.* Mobilization of the colon and rectum after initial laparotomy for all these procedures was similar (*Figure 1a*). The sigmoid was fully mobilized after division of the congenital adhesions. The dissection was carried on round the extraperitoneal rectum to the level of the pelvic floor; Denonvilliers' fascia was divided well above the seminal vesicles in men to avoid injury to the nervi erigentes. The lateral ligaments were always divided.

In the suture rectopexy group, after full mobilization, four non-absorbable sutures (Prolene®; Ethicon Ltd., Edinburgh, UK) were used to fix the rectum to the pelvic floor and presacral fascia (*Figure 2a*).

In the group undergoing posterior Ivalon sponge rectopexy, the procedure followed was as described in 1959 by Wells[11]. Ivalon® (polyvinyl alcohol sponge; Downs Surgical Ltd., UK) was secured to both the rectum and the presacral fascia (*Figure 2b*) by non-absorbable sutures. The rationale for using Ivalon lies in the dense fibrous reaction it produces, resulting in firm fixation of the rectum within the sacral curve. The Ivalon itself is considered to be absorbed over a number of years[12].

The anterior and posterior Marlex rectopexy procedure is similar to that described by Nicholls and Simson[13]. In addition to the sheet of Marlex® mesh (C. R. Bard Incorporated, Massachusetts, USA) sutured posteriorly, a strip of the material was also placed in the rectovaginal septum to provide greater support anteriorly (*Figure 2c*).

*Resection and rectopexy.* The technique adopted was modified from that of Frykman and Goldberg[14]. The extent of the rectal and colonic dissection and the resection lines are shown in *Figure 1b*. The splenic flexure was always mobilized; we believe that this ensures that healthy well vascularized descending colon is used for the anastomosis rather than the sigmoid, which is often diverticular and which may have a poor blood supply. As previously noted, the lateral ligaments were always divided. The colorectal anastomosis was performed without tension where convenient, usually at about 12 cm from the anal verge (*Figure 2d*). Low anastomosis was avoided. Finally, the lower rectum was fixed with non-absorbable sutures to the pelvic floor and presacral fascia.

## Results

Patient age, duration of symptoms and length of follow-up were similar for the different procedures (*Table 1*). Initially older patients were selected for simple suture rectopexy because it is a less extensive procedure. With increasing experience we have been happy to resect even in the elderly. In all cases the prolapse was well controlled by surgery and there has been no significant morbidity and no deaths. Furthermore, there has been no

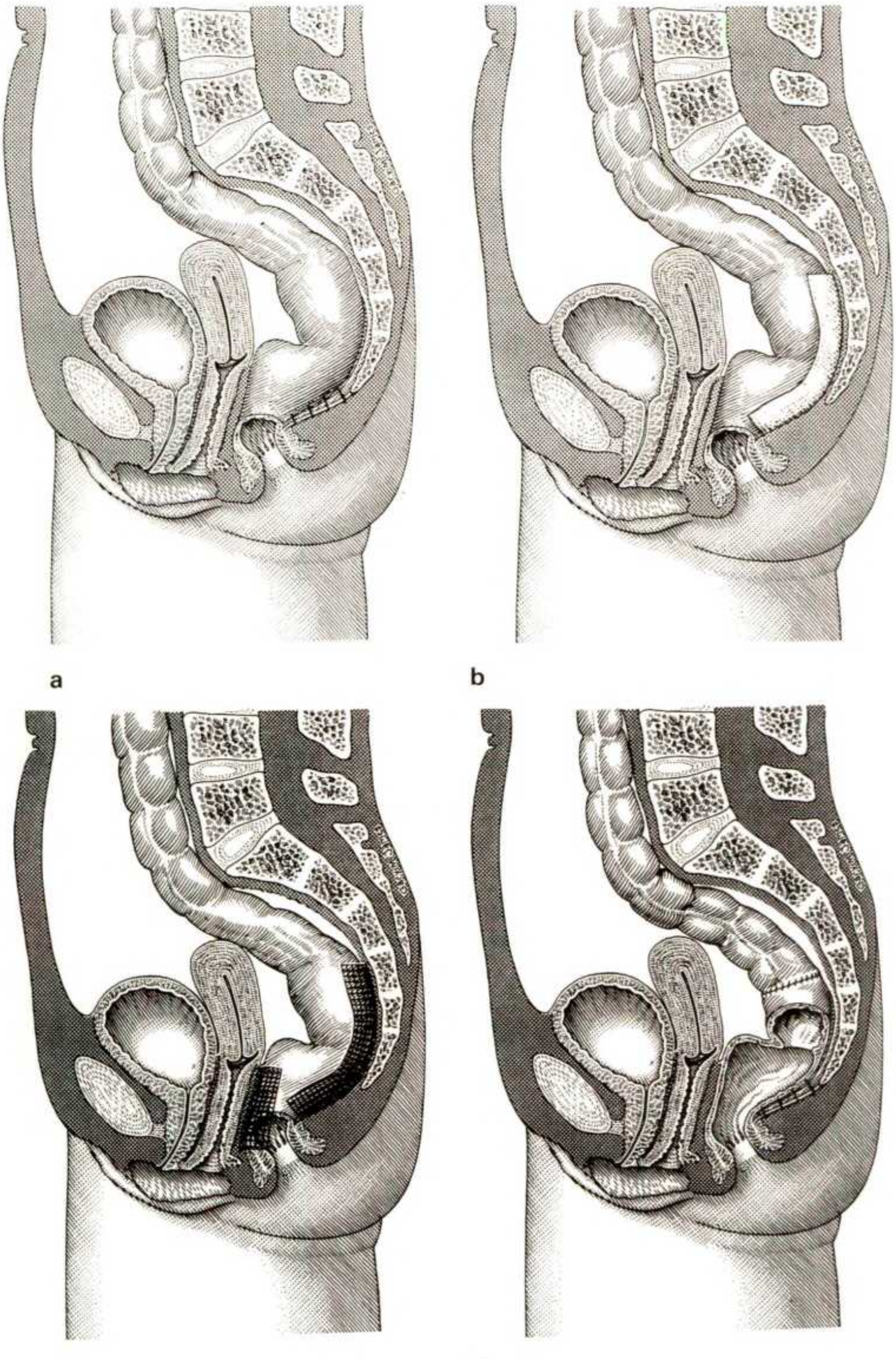

**Figure 2** **a** *Simple suture rectopexy. Four sutures fix the rectum to the presacral fascia.* **b** *Posterior Ivalon sponge rectopexy.* **c** *Anterior and posterior Marlex rectopexy.* **d** *Resection and rectopexy. The rectum is sutured as in* **a**, *but the sigmoid colon and upper rectum have been excised with colorectal anastomosis*

anastomotic breakdown, nor has any prosthetic material needed to be removed. Three patients in the Marlex group and three in the resection group had slow transit constipation as defined by retention of $>20$ per cent of ingested markers at 5 days[9].

Bowel frequency was not significantly altered in any of the groups (*Table 2*), nor was there any indication that postoperative constipation was a problem, as incomplete evacuation and straining at stool were unchanged by operation, except that in the resection group emptying was significantly improved. None of our patients required regular laxatives as a consequence of the surgery, but many remained on a high-fibre diet to maintain a regular bowel habit.

Continence was significantly improved in all except the Ivalon group. This was most marked after resection and suture procedures. In the patients in whom continence was successfully restored, straining at stool was significantly reduced after operation in the resection and rectopexy group ($0\cdot01 < P < 0\cdot05$), but not after any other procedure. The awareness of the call to stool was unaffected by surgery.

### *Anal manometry*

*Table 3* shows the paired preoperative and postoperative manometric data. There was a significant rise in the resting anal canal pressures in the resection group (*Figure 3*) and the

**Table 2** *Functional outcome after four types of rectopexy*

| | Continence to solid and liquids | | Bowel frequency (per day) | | Straining at stool | | Incomplete emptying | |
|---|---|---|---|---|---|---|---|---|
| | Preop. | Postop. | Preop. | Postop. | Preop. | Postop. | Preop. | Postop. |
| Suture rectopexy ($n = 10$) | 2 (20) | 9 (90)* | 2·5 (0·5–5) | 1·5 (1–3) | 5 (50) | 4 (40) | 5 (50) | 2 (20) |
| Ivalon rectopexy ($n = 9$) | 4 (44) | 6 (67) | 1 (0·5–3) | 1·5 (1–5) | 7 (78) | 4 (44) | 6 (67) | 5 (56) |
| Marlex rectopexy ($n = 20$) | 5 (25) | 15 (75)† | 3 (0·1–5) | 1·75 (1–5) | 13 (65) | 11 (55) | 13 (65) | 8 (40) |
| Resection rectopexy ($n = 29$) | 6 (21) | 24 (83)‡ | 1·5 (0·1–6) | 2 (0·5–5) | 22 (76) | 17 (59) | 16 (55) | 9 (31)* |

Bowel frequencies are median (range); all other values are number (percentage) of patients. *$P < 0·05$; †$P < 0·01$; ‡$P < 0·001$ (Wilcoxon's paired signed rank test)

**Table 3** *Manometric data before and after rectopexy by four techniques*

| | Suture rectopexy | | Ivalon rectopexy | | Marlex rectopexy | | Resection rectopexy | |
|---|---|---|---|---|---|---|---|---|
| | Preop. | Postop. | Preop. | Postop. | Preop. | Postop. | Preop. | Postop. |
| Sphincter length (cm) | 3<br>(1–4) | 3<br>(2–3·5) | 3<br>(2–4) | 3<br>(2·5–4) | 3<br>(0–4) | 3<br>(0–4) | 3<br>(0–4) | 3<br>(1–4) |
| Maximum resting pressure ($cmH_2O$) | 25<br>(10–100) | 55<br>(20–100) | 60<br>(35–85) | 55<br>(30–125) | 60<br>(20–160) | 52<br>(20–125) | 45<br>(12–145) | 65<br>(25–185)* |
| Maximum voluntary contraction ($cmH_2O$) | 90<br>(40–200) | 87<br>(40–175) | 180<br>(70–295) | 135<br>(85–313) | 113<br>(45–265) | 115<br>(30–225) | 115<br>(32–215) | 110<br>(50–230) |

Values are median (range). *$P < 0·001$ (Wilcoxon's paired signed rank test)

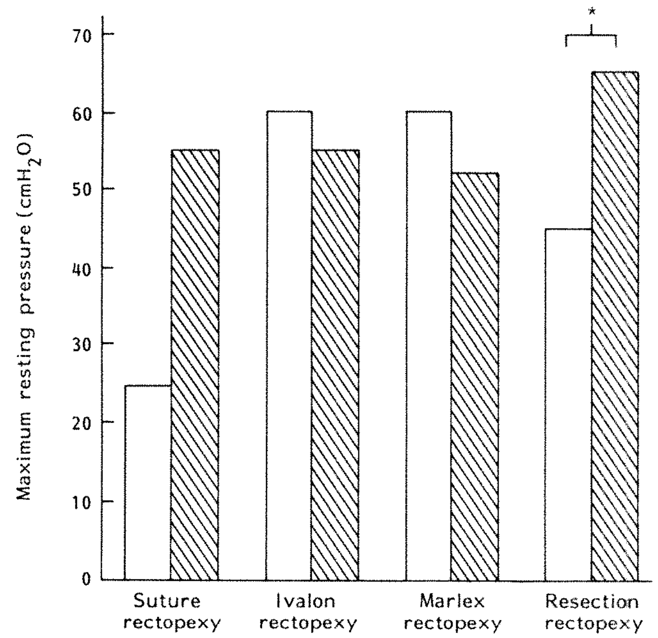

**Figure 3** *Changes in maximum resting pressure before (☐) and after (▨) operation. *There was a significant improvement over preoperative values after resection and rectopexy* (P < 0·001, *Wilcoxon's paired signed rank test*)

same trend towards improvement was seen in the suture group, although this did not achieve statistical significance. There was no significant alteration in pressures in the implant groups. Indeed, there was a trend towards reduction in anal pressures after Marlex and Ivalon rectopexy.

In addition, the improvement in continence for all patients was correlated with the preoperative resting pressure ($r_S = -0·32$, $P = 0·008$; *Figure 4*) and with the improvement in resting pressure after operation ($r_S = 0·26$, $P = 0·034$; *Figure 5*).

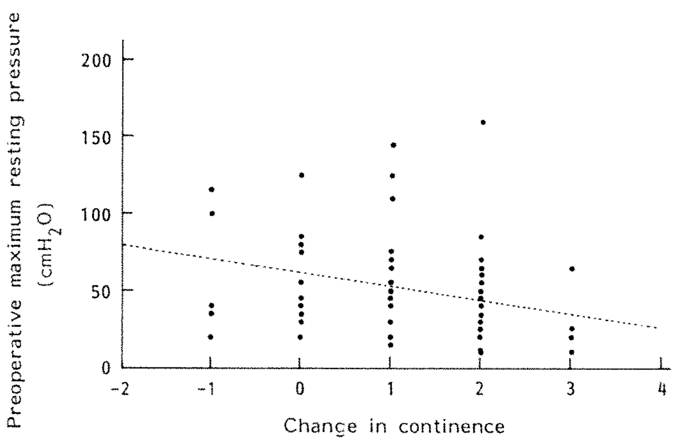

**Figure 4** *Preoperative resting pressure correlates inversely with change in continence.* $r_S = -0·32$, $P = 0·008$ *(Spearman's ranked correlation test)*

### *Anorectal sensation*

Rectal sensation was assessed in only three patients in the suture and Ivalon groups, and hence no data are presented (*Table 4*). The volume required to produce a sensation of rectal filling was reduced in the other two groups but reached statistical significance only in the resection group.

Lower and mid-anal canal sensation was unchanged except in the Ivalon and suture groups. However, if the patients in whom continence was restored were analysed separately, mid-anal canal sensitivity was also improved in those undergoing Marlex or resection rectopexy ($P < 0·05$). In the upper anal canal, sensation was improved in all except the Marlex group; similarly, those with restored continence in this group and the other three groups showed significant improvements ($P < 0·01$). Despite these significant improvements, there was no direct correlation between improved sensation and restoration of continence.

**Table 4** *Sensory data before and after rectopexy*

| | Suture rectopexy | | Ivalon rectopexy | | Marlex rectopexy | | Resection rectopexy | |
|---|---|---|---|---|---|---|---|---|
| | Preop | Postop. | Preop. | Postop | Preop. | Postop. | Preop. | Postop |
| First rectal sensation (ml) | n.d. | n.d. | n.d. | n.d. | 65 (10–415) | 50 (10–300) | 53 (10–250) | 35 (10–100)* |
| Anal sensation (mA) | | | | | | | | |
| Lower | 8·4 (3–26) | 7·5 (3–26) | 8 (3–19) | 6·3 (2–11) | 7·5 (2–20) | 7·5 (1–14) | 9 (3–26) | 7 (4–14) |
| Middle | 9 (6–26) | 7·5 (3–15)* | 9 (3–26) | 7·3 (3–12)* | 9 (2–26) | 9 (3–22) | 10 (4–25) | 8 (3–15) |
| Upper | 23 (5–26) | 12·5 (9–23)* | 15 (3–26) | 11 (4–23)* | 17 (3–26) | 13 (3–26) | 15 (5–26) | 13 (1–24)† |

Values are median (range) n.d., Not done; *$P < 0·05$, †$P < 0·01$ (Wilcoxon's paired signed rank test)

**Table 5** *Radiographic changes after Marlex and resection rectopexy*

| | Marlex rectopexy | | Resection rectopexy | |
|---|---|---|---|---|
| | Preop. | Postop | Preop | Postop |
| Anorectal angle (degrees) | | | | |
| At rest | 104 (81–123) | 125 (98–138)* | 92 (89–146) | 112 (93–135) |
| On contraction | 91 (72–116) | 105 (95–138)* | 92 (83–137) | 104 (95–130) |
| During straining | 117 (76–140) | 137 (74–160)* | 113 (97–148) | 135 (89–144) |
| Perineal descent (cm) (negative result means below pubococcygeal line) | | | | |
| At rest | −1·1 (0 to −2·2) | −1·1 (0 to −2·6) | −1 (−3·9 to 1·8) | −1·8 (0 to −4·5) |
| On contraction | −1·2 (0·2 to −3) | −0·2 (−3·7 to −1·2)* | −1 (−4 to 0·5) | −1·8 (−5 to −0·2) |
| During straining | −4·5 (−6·6 to −1·5) | −2·7 (−6·8 to −0·1) | −3·2 (−9·7 to −1·5) | −4 (−6·3 to −0·3) |

Values are median (range) *$P < 0·05$ (Wilcoxon's paired signed rank test)

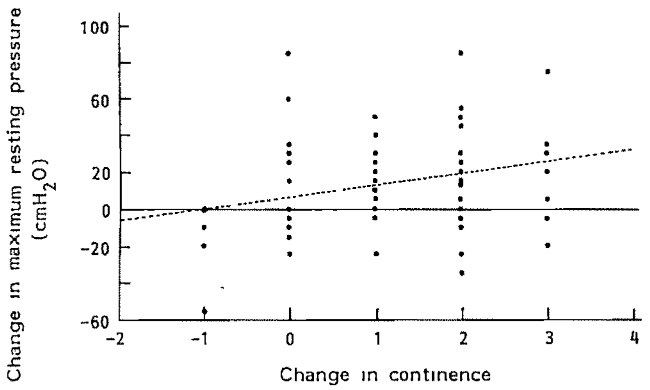

**Figure 5** *Improvement in continence correlates with improvement in maximum resting pressure* $r_s = 0·26$, $P = 0·034$ *(Spearman's ranked correlation test)*

*Proctography*

Radiological correlations were unhelpful in predicting the success of the prolapse repair or the return of continence *Table 5* shows a significant opening of the anorectal angle associated with Marlex rectopexy and a similar trend was seen in the resection group. On contraction, the pelvic floor was significantly higher after Marlex rectopexy but there were no significant changes in the other measurements of pelvic descent.

## Discussion

Transabdominal rectopexy is the operation of choice for the control of complete rectal prolapse in patients fit enough for an abdominal procedure. There are various techniques available which, in addition to correcting the procidentia, restore continence in the majority of individuals with prolapse and incontinence[15,16]. The majority of authors use some form of prosthetic material to induce fibrosis and ensure fixation[17–21]. There is, however, a recognized incidence of sepsis[22] in relation to the use of prosthetic material, which we have not to date encountered in our series. It has also been suggested that absorbable mesh may be appropriate and may reduce the risk of sepsis without increasing the recurrence rate[23]. The argument in favour of synthetic implants is the low recurrence rate after their use and the reported higher incidence of recurrence for fixation-only procedures.

Disordered bowel habit is considered to be one of the predisposing factors in the aetiology of prolapse, and was considered to have contributed to recurrences in one series[19]. Furthermore, since constipation frequently complicates both Ivalon[3] and Marlex rectopexy, there is a case for adopting an operation which specifically aims to minimize this complication. This series describes the progression and evolution of our practice from prosthetic to non-prosthetic rectopexy and as such is not a randomized trial. There was initially a tendency to select suture rectopexy for patients considered to be at risk from a more extensive procedure, but with experience this selection has been found to be unnecessary.

The precise mechanism of constipation following rectopexy is uncertain. Most previously reported studies have not carried out preoperative transit studies, so those reporting a high incidence of constipation may have contained numbers of subjects with slow transit. However, this cannot account for all the reports of postoperative constipation, and the operation may be responsible in some way. High fixation of the rectum allows the redundant sigmoid colon to prolapse into the pouch of Douglas and may create a mechanical obstruction at this site. Indeed, Ripstein has now abandoned Marlex encirclement in favour of posterior fixation; the original Ripstein procedure was complicated by a 16·5 per cent incidence of faecal impaction[24] Despite this modification, if the sigmoid is redundant it may still be kinked at its junction with the rectum However, Mann and Hoffman[3] reported that almost 50 per cent of their patients had troublesome constipation after posterior Ivalon rectopexy. An alternative hypothesis is that the rectal mobilization divides the parasympathetic neural inflow to the left colon through the pelvic autonomic fibres, thereby altering bowel function

Resection rectopexy as advocated by Frykman and Goldberg[14] aims to prevent constipation by removing the partially denervated sigmoid and avoiding rectosigmoid distortion, which besets the fixation procedures They also advocate low fixation, primarily to re-create the anorectal angle. Although we would not consider the angle to be of major importance in restoring continence[25], low fixation does avoid distorting the anatomy. In addition, the Mayo Clinic group has for many years advocated high anterior resection without fixation[26]. Clearly, simple sigmoid resection is not a good procedure for treating severe constipation, but as these groups did not find constipation to be a problem after operation there may be a good case for adopting routine resection. In addition, the long-term recurrence rates are among the lowest reported[2].

We were initially concerned that diarrhoea might be a consequence and that this could cause incontinence, but this did not prove to be the case. The major drawback of the resection procedures is the risk of anastomotic leakage. For this reason we prefer to mobilize the splenic flexure routinely and to use well vascularized descending colon for the anastomosis We have had no anastomotic complications using this technique. We avoid low anterior resection with its increased propensity to leakage, and consider this to be an irrational operation because it removes the compliant rectal reservoir, which we believe is an important component of the continence mechanism. Removal of the rectum and its replacement by non-compliant and often diverticular sigmoid may explain the lower continence rates after perineal rectal excision for prolapse Certainly it may be appropriate to perform resection and rectopexy in patients with preoperative constipation, and in fact the resection may be usefully extended to good effect in those with proved delayed colonic transit[2].

The incidence of restored continence associated with successful prolapse repair is generally high[16,18,19,27,28], and a proportion of those with persistent incontinence may be helped by postanal repair[20]. In our experience, continence was restored in the majority of patients in all operative groups, although interestingly this was more marked in the resection and rectopexy group compared with the prosthetic operations. This seems to suggest that restoration of continence is not dependent on the induction of postoperative constipation. In fact, in all our groups, there was a trend to fewer features of constipation. Straining at stool was most reduced after Ivalon and resection rectopexies, and a feeling of incomplete evacuation improved after all rectopexies. All but the resection procedures have been considered to increase constipation[3]. Sayfan *et al.* reported an increase in constipation after posterior Marlex rectopexy and a reduction after resection rectopexy[29]. It may well be that, in patients without preoperative constipation, the risks of an anastomosis have to be balanced against the risks of sepsis from prosthetic implants in coming to a decision about the type of procedure to select. We also recommend that colonic transit studies to diagnose delayed transit should be performed as a routine before all procedures, because this may affect the choice of procedure.

Both anal sphincter and pelvic floor muscle impairment are well known features of prolapse[30], and there is good evidence of somatic denervation, both histologically[31] and electromyographically[32]. Internal (visceral) anal sphincter function is also impaired and recovery of function has been cited as a major factor in improved continence[4,30,33]. It seems probable that this impaired function is related to activation of the rectoanal inhibitory reflex by the advancing prolapse. We have recorded significant improvements in resting pressures after resection and rectopexy and have seen a similar trend after suture rectopexy, which suggests that recovery of the internal anal sphincter was important in the restoration of continence. Keighley *et al.* have reported a series with no evidence of sphincter recovery[20], but they used a Marlex implant. Our study is in agreement with their findings in that we did not record an improvement in resting sphincter pressures in the Ivalon and Marlex groups. The reasons for these differences are unclear and it could be that the implants, by producing an intense tissue reaction, prevent recovery of internal anal sphincter function. This is an important finding, and clearly warrants further investigation. Recovery of continence is obviously complex and multifactorial and cannot be dependent only on internal sphincter recovery or we would have poorer results in the implant groups. It is possible that with larger numbers the improved physiological results would demonstrate a definite advantage for avoiding implants. We could not explain recovery of continence in our implant patients on the basis of improved anal pressures; the only measurement that improved was anal sensation, which would make patients more aware of impending leakage

It is interesting to note the correlations between the recovery of continence and initial sphincter pressures. This suggests that the preoperative pressures reflect the degree of sphincter inhibition and that patients with the lowest sphincter pressures have potentially the most to gain in terms of improvement of continence once the sphincter inhibition is removed. This finding is contrary to that of one other study[34], but our observations seem to be confirmed by the correlation of improved continence with improvement in resting sphincter pressure.

Spencer[35] suggested that rectoanal inhibition, combined with a failure to appreciate descent of the prolapse because of poor sensation, was an important aetiological factor in incontinence. Our patients show reduced rectal awareness compared with normal controls ($P < 0{\cdot}01$) and, although there was some evidence of recovery of rectal sensation in the postoperative period, this seems unlikely to be instrumental in restoring continence *per se*. In addition, we have recorded significantly improved sensitivity in the upper and mid-anal canal, which are the important areas for discrimination of rectal contents during the sampling reflex[36]. This overall improved anorectal sensation may have an important role to play in improved postoperative continence, and we believe that successful rectopexy may work by restoring normal upper anal and lower rectal anatomy, thus allowing a return to more normal function. There does not, however, seem to be any direct correlation between the recovery of continence and the improvement in sensation. Despite this we believe that the recovery of sensation and recovery of the sphincter allow a more appropriate response to any perceived threat to continence.

Unlike Yoshioka *et al.*[37], we have found no predictive value in assessing radiological parameters · either anorectal angles or perineal descent. In fact, in our series, there was significant opening of the anorectal angle in the postoperative period, which confirms previous observations that the acuity of the anorectal angle has little to do with continence[25]. We have also reported a lack of correlation between radiological findings and recovery of continence after sphincter repair[38].

In conclusion, restoration of continence and correction of the prolapse is satisfactory after any of these abdominal procedures. Constipation does not seem to be the underlying reason for recovery of continence, whereas sphincter recovery and perhaps improved sensory awareness have important roles to play For patients with evidence of preoperative constipation, resection and rectopexy seems most logical, but for all other patients a balance must be struck between the minimally higher risk of recurrence in simple suture rectopexy, the risk of sepsis and slightly poorer improvements in bowel function with the implant procedures, and the risk of anastomotic complications with resection and rectopexy. We currently favour resection and rectopexy, and reserve suture rectopexy for those at risk from a longer and more complicated procedure.

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# Function of the distal rectum after low anterior resection for carcinoma

*From a personal series of 232 anterior resections performed over 10 years, functional results have been analysed in two specific groups of patients: those with anastomoses 3 cm* (n = *26) and 6 cm* (n = *42) from the anal verge. In both groups low anterior resection had been performed with total mesorectal excision. Function was assessed in four categories: bowel frequency, ability to distinguish flatus from faeces, ability to defer defaecation, and frequency of soiling. Independent analysis of the 3 cm group showed a significant deterioration in function in each category after operation. The ability to defer defaecation and the frequency of soiling were unchanged after operation in the 6 cm group, and these functions were significantly better than in the 3 cm group. On the basis of these results, patients undergoing low anterior resection with total mesorectal excision should benefit from the preservation of a short segment of distal rectum, provided that the distal resection margin is not compromised.*

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Anterior resection for low rectal cancer is appropriate provided total mesorectal excision (TME) is performed[1] and an adequate distal bowel clearance[2,3] is achieved. Although there should be no compromise on the distal resection margin, there have been suggestions[2,3] that the standard requirement for 5 cm distal clearance can be reduced to 2 cm without any increase in local recurrence rates. Recently it has been shown[4] that there is no significant difference in local recurrence rates in patients undergoing anterior resection with TME when the resection margin is < 1 cm, compared with a resection margin > 1 cm.

The technique of TME has been described elsewhere[1,5]. It has been the practice in this unit to preserve as much distal rectum as possible in the belief that this would minimize any detrimental effect on continence and function. This study assessed whether preservation of the distal few centimetres of rectum affects functional results in uncomplicated low anterior resection.

## Patients and methods

### *Patients*

Since 1978, prospective records have been kept of 232 consecutive anterior resections peformed by one author (R J H ) or under his close supervision. Extensive 3-monthly follow-up has included rectal examination and endoscopy by a consultant oncologist and surgeon with data recording by a full-time research assistant.

In this series 208 patients underwent TME. The 5-year local recurrence rate was 3 per cent in patients classified as having undergone curative resections[4]. Anastomotic height varied from 0 5 to 12 cm from the anal verge.

Two groups of patients were identified with stapled anastomoses 2·5–3·5 cm (median 3·0 cm) and 5·5–6·5 cm (median 6 0 cm) from the anal verge. All patients had undergone TME. Functional results were assessed by means of a questionnaire. Where doubt remained, assessment was completed by telephone or in the clinic.

The 3 cm group comprised 26 patients. Forty-five patients had initially undergone a stapled anterior resection, with end-to-end anastomosis 2·5–3 5 cm from the anal verge, but 18 had died by the time the study was carried out. Of the 27 who were alive, all of whom replied, one was excluded because anastomotic leakage had occurred after operation This patient was excluded in the belief that subsequent fibrosis consequent upon leakage might affect continence

The 6 cm group comprised 42 patients. Although 88 patients had initially undergone a stapled anterior resection with end-to-end anastomosis 5·5–6·5 cm from the anal verge, 32 had died by the time of this study. Of the 56 patients who were alive, 14 were excluded for the following reasons· failure to reply in eight (response rate 86 per cent), anastomotic leakage in five, evidence of local recurrence in one

### *Questionnaire*

Questions were framed to yield information on bowel frequency, the ability to distinguish flatus from faeces, the ability to defer the call to stool for 10–15 min, and the frequency of faecal soiling. The questionnaire was divided into two parts dealing with symptoms before and after the operation The questions in both parts were

1. How often did/do you open your bowels?
2 Did/do you have difficulty deciding between wind and bowel motion? Yes/No
3 If you felt/feel the urge to open your bowels could you hold on and stop it for 15 minutes? Always/Sometimes/Never
4 Did/do you soil your underclothes? Never/Sometimes/Always

### *Statistical methods*

Ordinal data were not normally distributed and are therefore expressed as median (range) and analysed using the Mann–Whitney $U$ test. Nominal data were analysed using Fisher's exact test Significance was assumed when $P < 0 05$.

## Results

*Table 1* shows that there was no significant difference in the median age at operation, sex distribution or survival. The

**Table 1** *Preoperative and operative characteristics of patients and tumours*

| | 3 cm group ($n$ = 26) | 6 cm group ($n$ = 42) |
|---|---|---|
| Age at operation (years) | 64 2 (43–84) | 66 0 (38–84) |
| Sex ratio (M:F) | 14 12 | 24·18 |
| Survival (years) | 3 5 (0 2–10 2) | 4·5 (0·6–11 2) |
| Sigmoidoscopic height (cm) of tumour before operation | 4 5 (3 5–10 0) | 9·0 (7·0–13 0)* |
| Dukes' classification (A B C) | 11 6 9 | 7:21:14† |
| Distal margin (cm) | 0 5 (0 5–7 0) | 3·5 (1 0–7 0)* |
| Anastomotic height (cm) | 3·0 (2 5–3 5) | 6·0 (5·5–6·5) |
| Anastomosis with splenic flexure:sigmoid colon | 19 7 | 32.10 |

Values other than ratios are median (range). *$P < 0 05$ (6 cm group *versus* 3 cm group, Mann–Whitney $U$ test); †$P < 0·05$ (6 cm group A:B *versus* 3 cm group A:B, Fisher's exact test)

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**Table 2** *Anal function in the 3 cm and 6 cm groups before and after operation*

| | 3 cm group | | 6 cm group | |
|---|---|---|---|---|
| Questions | Preoperative | Postoperative | Preoperative | Postoperative |
| Median bowel frequency/day | 1 (1–4) | 3 (1–8)* | 1 (1–3) | 3 (1–6)* |
| Difficulty distinguishing flatus from faeces, no:yes | 22:4 | 15:11† | 34:8 | 26:16† |
| Defer the urge for 15 min, always occasional and never | 19:7 | 9:17† | 28:14 | 25:17‡ |
| Soiling, never:occasional | 17:9 | 8:18† | 28:14 | 23:19‡ |

Values in parentheses are ranges $*P < 0{\cdot}05$ (postoperative *versus* preoperative, Mann–Whitney $U$ test); $†P < 0{\cdot}05$ (postoperative *versus* preoperative, Fisher's exact test), $‡P < 0{\cdot}05$ (postoperative 6 cm group *versus* postoperative 3 cm group, Fisher's exact test)

median sigmoidoscopic height of the tumour was significantly greater in the 6 cm group. As expected, the 3 cm group had a significantly smaller median resection margin than the 6 cm group ($P < 0{\cdot}01$). The ratio of patients with Dukes' A classification tumours to those with Dukes' B tumours was significantly higher in the 3 cm group. There was no difference between the groups over the use of the splenic flexure *versus* the sigmoid colon for the anastomosis, although on review of the entire series the risk of leakage has been shown to be higher when the sigmoid is used[6].

### *Functional results*

In the 3 cm group there was a significant deterioration in function after operation in all four categories (*Table 2*). There was an increase in bowel frequency and fewer patients could distinguish flatus from faeces after operation. Fewer patients could defer the call to stool and more patients soiled.

In the 6 cm group there was a significant deterioration in function after operation in two of the four categories. Although there was a significant increase in bowel frequency and significantly fewer patients could distinguish flatus from faeces after operation, there was little change in the number of patients who could defer the call to stool and in the proportion of patients who soiled.

The postoperative results for the four parameters of anal function outlined above were compared (*Table 2*). There was no significant difference between the two groups in postoperative bowel frequency and in the proportion of patients able to distinguish flatus from faeces. However, a significantly greater proportion of patients in the 6 cm group could both defer the call to stool for 15 min and never suffered from faecal soiling.

## Discussion

It was shown by Goligher and Hughes[7] that distension of the rectum caused a sensation of fullness in the rectum, but that distension higher than 15 cm from the anal verge led to a feeling of intestinal colic. Parks *et al.*[8] confirmed earlier findings of perpetual tonic activity in the external sphincter of humans and also showed that increasing rectal distension inhibited the tonic activity of the voluntary sphincter after an initial excitatory phase. They postulated the presence of receptors in the rectal wall, although in a careful histological study Duthie and Gairns[9] had demonstrated a dearth of sensory receptors in the rectum and an abundant supply in the upper anal canal.

Goligher[10] stressed the importance of preserving 6–8 cm of anorectal stump during sphincter-saving resections if sensory incontinence was to be avoided He later showed that a rectal type of sensation might develop when a coloanal anastomosis was fashioned[7], postulating that this might be due to pressure of a distended colon on adjacent pelvic structures. Subsequently, Lane and Parks[11] assessed patients with coloanal anastomoses and suggested that the rectum was not essential for the appreciation of impending evacuation or for the sphincter inhibitory reflexes.

The two groups studied here were similar with regard to age, sex distribution, survival rate, type of resection performed and method of reconstruction. As expected, the 3 cm group had significantly lower tumours before operation, with a higher ratio of patients with Dukes' A classification tumours to those with Dukes' B tumours and a significantly smaller distal resection margin. The latter probably represents an operative factor in that TME is followed by the placement of two fingers distal to the tumour before a right-angled clamp may be safely applied. A tumour at an earlier stage is likely to be smaller and therefore need a shorter distal resection margin

In the first part of this study, functional results are analysed within each group after low anterior resection. In both groups there was a deterioration in function after operation in all four categories assessed.

Comparison of the 3 cm and 6 cm groups after operation showed no statistically significant difference in bowel frequency and the ability to distinguish flatus from faeces. However, preservation of the distal rectum in the 6 cm group improved the ability to defer the call to stool and reduced the incidence of soiling. The latter effects may be due to a reservoir effect of the terminal rectum or more complete preservation of the sensitive upper anal canal. These results suggest that preservation of a short segment of distal rectum improves functional results and that as much as possible of the lower rectum should be preserved.

TME is the cornerstone of safe anterior resection[1,12] for carcinoma. It involves excision of most of the rectum, together with its lymphatic and vascular mesentery, by cleavage of the embryological plane between the hindgut and pelvic nerves[13]. This leaves a hollow sacrum down to the puborectalis sling with a small protruding stump of rectum on to which the colon may be anastomosed. The procedure appears justified by our low local recurrence rates of 3–3·6 per cent for curative anterior resection[4,13] Many surgeons may regard the dissection as easier if TME is concluded by dividing the distal mesorectum at the anorectal junction. Once the rectum and mesorectum have been completely mobilized, however, both structures stretch and the mesorectal tail becomes a slender fatty surround tapering towards the muscle tube posteriorly and laterally. A few scissor cuts are sufficient to peel up the tail so that a right-angled clamp at around 6 cm need only occlude muscle. In this way a useful short segment of distal rectum may be preserved and the whole mesorectum may still be removed with the specimen The improvement in functional results reported here appears to justify conservation of the distal rectum when the position of the primary tumour permits.

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## For debate

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# Informed consent in surgical research

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At the July 1990 meeting of the Surgical Research Society in Southampton, UK, a symposium was held to discuss ethical issues in surgical research. It was suggested that informed consent should be obtained for any procedure that exceeded standard clinical management. The primacy of the patient's decision to participate in the research was emphasized. Some of the ethical issues and practical difficulties have been discussed elsewhere[1]. This article considers current practice in surgical research in the UK.

At that meeting of the Society there were 40 papers which described observations made in patients or normal subjects. A questionnaire was sent to the first author of each paper; 36 replied. The authors described their work in the following terms: (1) observation of clinically indicated investigations, two; (2) extensive investigations of a specific patient group, eight; (3) assessment of a new technique or investigation, 14; (4) comparison of different treatments, seven; and a combination of (3) and (4) in five cases Controls were used in 24 of the studies. The level of informed consent varied from no consent at all to full written informed consent (*Table 1*). Clearly the investigators had made a judgement of the degree of departure from normal clinical practice, and of the effects on the patients of the information required for informed consent. The studies in which consent was not obtained included two in which clinically indicated investigations were recorded, four in which a new technique or investigation was assessed, and one in which a comparison of different treatments was made. Brief verbal explanation was given with implied consent in one study in which controls were subjected to extensive investigations, four studies which involved assessment of a new technique or investigation, and two comparisons of different treatments.

**Table 1** *Level of consent obtained in 36 studies (24 with control subjects)*

| | Patients/subjects | Controls |
|---|---|---|
| None | 7 (19) | 5 (21) |
| Brief verbal explanation – consent implied | 6 (17) | 4 (17) |
| Full explanation – express verbal consent | 14 (39) | 8 (33) |
| Written | 9 (25) | 7 (29) |

Values are numbers of studies (percentages)

Several studies were conducted without consent or with inadequate consent. One investigator commented that his study involved collection of small additional samples during operation and so informed consent was inappropriate. This belief is incorrect. In an age when the primacy of patient choice is recognized, the investigator must consider all the potential consequences of including a patient in a study, even if this involves only a minute departure from normal practice. Although complications from the collection of study samples are extremely unlikely, one might be required to explain how, for example, a glass slide for cytology samples broke and pieces of glass were retained in the wound, or how an inadvertent air embolus was caused during collection of an additional blood sample. Furthermore, the investigator could face a moral dilemma· if information obtained through the study might indicate a different prognosis, should the patient be told of this 'experimental' data? Is it scientifically correct to include this 'experimental' information in planning management?

Clinical investigation imposes higher standards of consent than are usual in day-to-day practice. A surgeon who uses a new technique on the basis of his or her clinical instinct can do so within the usual standards of clinical consent. An investigator, who wishes fully tc assess the same technique and perhaps to perform additional investigations to make this assessment, is required to provide the patient with a full explanation of his or her intentions. When choosing between different treatments the clinician needs only to inform the patient that a treatment will be given, whereas the investigator must outline the options and the random or other nature of the choice of options. These points were made at the symposium on ethical issues at the Southampton meeting of the Surgical Research Society The survey showed that there were some in the audience who were in a position to learn from that discussion In the UK the standards of obtaining informed consent in surgical research are high, but we cannot claim universal acceptance of the patient's overriding right to choose whether or not to take part in clinical investigations

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# Prognostic factors from computed tomography in acute left colonic diverticulitis

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*This prospective study examined factors which may predict a poor outcome (complications and recurrence) after a first attack of diverticulitis which has been successfully managed conservatively. Twenty-four of 107 patients who entered the study had a poor outcome: persistent diverticulitis (nine cases), recurrence (seven cases), colonic stenosis (six cases), residual parasigmoid abscess (one case) and colovesical fistula (one case). Eight of the 18 men aged 50 years or less had a poor outcome compared with 16 of the remaining 89 patients* ($P = 0{\cdot}032$). *Twelve of 76 patients (16 per cent) with mild findings on computed tomography (CT) (localized thickening of colonic wall and inflammation of pericolic fat) had a poor outcome compared with 11 of 23 patients (48 per cent) whose CT was estimated as severe (abscess and/or extraluminal air and/or extraluminal Gastrografin®)* ($P = 0{\cdot}004$). *These results suggest that elective colectomy can be proposed after a first attack of acute left diverticulitis in men up to 50 years of age and/or in patients whose initial CT reveals findings of severe diverticulitis.*

Colonic diverticulosis is common and is found in approximately half of people aged over 60 years. Only 10 per cent develop symptoms related to diverticula[1]. There is no way of predicting these complications. If 'high-fibre' diets prevent diverticulosis, their role in diverticulitis remains unclear[2]. The place and timing of surgery after a first attack of diverticulitis which has been successfully managed conservatively is not defined.

This prospective study examined the factors that may predict a poor outcome and allow early elective one-stage colectomy for patients liable to develop recurrent or complicated diverticulitis.

## Patients and methods

From October 1986 to October 1990, all patients with a history and clinical findings suggestive of left-sided colonic diverticulitis underwent computed tomography (CT) and had a Gastrografin® enema (Schering Suisse AG, Schlieren, Switzerland) within 72 h of admission Patients were considered to have diverticulitis when one or both tests were diagnostic. Patients were excluded when both examinations were negative. Radiological criteria of acute diverticulitis and signs of severity provided by CT and Gastrografin enema are listed in *Table 1* CT used a high-resolution scan (fourth generation, 1200 SX type, Picker International, Highland, Ohio, USA) using 8 mm thickness and index couches with contrast orally and rectally; intravenous contrast was added when an associated abscess was suspected Interpretation of the scans was carried out by radiologists who were unaware of clinical details

Conservative treatment consisted of 10 days of intravenous antibiotics, active against Gram-negative and anaerobic bacteria, usually imipenem.

Patients were examined 3 months after the first attack with a barium double-contrast enema and pelvic CT, and were randomized to elective colectomy or conservative management This protocol applied to patients aged under 70 years with acceptable anaesthetic risks who showed complete resolution of their disease, clinically and radiologically. All gave oral consent. Randomization ceased in December 1989 when it was found that only four of 52 patients (8 per cent) had recurrent diverticulitis after a mean follow-up of 19 (range 4–38) months.

Patients who were still symptomatic 3 months after their initial attack and who presented with radiological complications such as stenosis, fistula and/or residual abscess were encouraged to undergo colectomy

Recurrence of diverticulitis was assessed when the patient presented with the same symptoms and clinical findings with at least one positive radiological examination (CT, Gastrografin enema or ultrasonography) Recurrence had to occur at least 3 months after the first episode, with an interval free from any abdominal symptoms Whenever possible, treatment was again conservative with 10 days of intravenous antibiotics Elective colectomy was then proposed

Groups of patients were compared using BMDP Statistical Software (BMDP Statistical Software Incorporated, Los Angeles, California/ University of California Press, Berkeley, California, USA)[3] with the $\chi^2$ test using Yates' correction when the minimal expected value was less than five.

One hundred and seven patients entered the study Fifty-seven patients were excluded from the study. 47 required surgery during their first stay and 10 were randomized to operation There were 47 men and 60 women with ages ranging from 23 to 92 years (mean 63 years). Twenty-five patients (23 per cent) were 50 years old or younger, men were significantly predominant in this subgroup (18 of 25 patients, $P = 0{\cdot}003$)

## Results

### *First hospitalization*

No patient died and the mean hospital stay was 13 (range 8–28) days

**Table 1** *Radiological criteria used to diagnose acute diverticulitis and assess its severity*

| | Mild diverticulitis | Severe diverticulitis |
|---|---|---|
| Computed tomography | Localized wall thickening (>5 mm)<br>Inflammation of pericolic fat | The same plus at least one of the following<br>Abscess<br>Extraluminal air<br>Extraluminal Gastrografin |
| Gastrografin® enema | Segmental lumen narrowing<br>Tethered mucosa<br>±Mass effect | The same plus at least one of the following<br>Extraluminal air<br>Extraluminal Gastrografin |

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*Clinical course after first hospitalization* (Table 2)

Patients had a mean follow-up of 24 (range 3–51) months.

Twenty-five patients underwent surgery, with no mortality. Sixteen of these had a complicated outcome and underwent mandatory surgery after 2–10 months for persistent diverticulitis (eight cases), symptomatic colonic stenosis at the 3-month control barium enema study (six cases), residual parasigmoid abscess (one case) and colovesical fistula (one case). Histological examination confirmed diverticulitis in all cases and acute inflammation in 13. Five patients without radiological evidence of residual diverticulitis were operated on for persistent pain (four cases) and unconfirmed parasigmoid abscess (one case); chronic diverticulitis was diagnosed in all five patients. Of these 21 patients, 13 were operated on within 3 months of the first attack and eight after 3 months (range 4–12 months).

Ninety-four patients had a follow-up of at least 3 months without further surgery (i.e. 107 patients minus 13 patients operated on within 3 months of the first attack). Seven of these 94 patients (7 per cent), four men and three women, had recurrent diverticulitis 10–24 months after the first attack (mean 16 months) which involved the same colon segment. All responded to medical therapy. Three underwent surgery after the second acute episode had subsided, three were unfit for surgery, and one refused surgery. Two of the four patients who were not operated on developed a second recurrence at 10 and 20 months after the initial attack; both responded favourably to conservative measures. The patient who refused surgery finally accepted a colectomy.

Seventy-eight patients (73 per cent) developed no complications and have not undergone surgery.

*Analysis of prognostic parameters* (Tables 3–7)

Twenty-four of the 107 patients (22 per cent) had a complicated outcome. seven developed recurrent diverticulitis, while 17 patients (mentioned above) continued to suffer from the same, radiologically documented, disease (persistent diverticulitis in nine cases, symptomatic colonic stenosis in six cases, residual parasigmoid abscess and colovesical fistula (one case each)).

Factors which appeared to predict a poor outcome after a first attack of acute diverticulitis which had been successfully treated medically were: (1) age and sex; and (2) initial radiological evaluation by CT and Gastrografin enema. The prognostic value of CT and Gastrografin enema was based on the possible presence of extraluminal air and/or extraluminal Gastrografin and/or abscesses, the latter seen on CT only (*Table 1*), all signs considered as severe. The numbers of patients having each type of investigation are shown in *Table 3*.

When the 24 patients with a poor outcome were compared with the other 83 patients, it appeared that complications were significantly more frequent in men aged 50 years or less ($P = 0{\cdot}032$) (*Table 4*); and that initial CT proved clearly

**Table 2** *Follow-up of 107 patients treated conservatively during first hospitalization*

| Surgery ($n = 25$) | | Conservative treatment ($n = 82$) | |
|---|---|---|---|
| Mandatory indications | 16* | Recurrence | 3* |
| Recurrence | 4* | Persistent diverticulitis | 1* |
| Debatable indications | 5 | No complication | 78 |

*Patients with a poor outcome

**Table 3** *Radiological investigation of 107 patients successfully treated conservatively for a first attack of diverticulitis*

| | No. of patients | No of patients with poor outcome | No. of patients with good outcome |
|---|---|---|---|
| Computed tomography + Gastrografin® enema | 101 (94) | 21 | 80 |
| Computed tomography | 105 (98) | 23 | 82 |
| Gastrografin enema | 103 (96) | 22 | 81 |

Values in parentheses are percentages

**Table 4** *Outcome of 107 patients whose first attack of diverticulitis was treated conservatively. Comparison between men aged up to 50 years and other patients*

| Subgroup | No. of patients with good outcome | No. of patients with poor outcome | Total | $P$* |
|---|---|---|---|---|
| Men aged ≤50 years | 10 (56) | 8 (44) | 18 | 0·032 |
| Men aged >50 years and women | 73 (82) | 16 (18) | 89 | |
| Total | 83 | 24 | 107 | |

Values in parentheses are percentages. *$\chi^2$ test with Yates' correction

**Table 5** *Prognostic assessment of 105 patients by computed tomography*

| | Total no. of patients* | No. of patients with poor outcome | $P$† |
|---|---|---|---|
| Computed tomography findings | | | |
| Severe | 23 | 11 (48) | 0·004 |
| Mild | 76 | 12 (16) | |

Values in parentheses are percentages. *Computed tomography was not diagnostic of diverticulitis in six cases, †$\chi^2$ test with Yates' correction

**Table 6** *Prognostic assessment of 103 patients by Gastrografin® enema*

| | Total no of patients* | No. of patients with poor outcome | $P$† |
|---|---|---|---|
| Gastrografin enema findings | | | |
| Severe | 9 | 3 (33) | 0·72 |
| Mild | 87 | 19 (22) | |

Values in parentheses are percentages. *Gastrografin enema was not diagnostic of diverticulitis in seven cases; †$\chi^2$ with Yates' correction

**Table 7** *Prognostic assessment of initial CT scan. Comparison between men aged up to 50 years and other patients*

| | No. of patients with 'severe CT' | No. of patients with poor outcome | No of patients with 'mild CT' | No. of patients with poor outcome | $P$† |
|---|---|---|---|---|---|
| Men aged ≤50 years ($n = 18$) | 8 | 5 | 10 | 3 | 0·37 |
| Men aged >50 years and women* ($n = 89$) | 15 | 6 | 66 | 9 | 0·045 |

*Of the 89 patients, 87 had an initial computed tomography (CT) evaluation and six CT scans were not diagnostic; †$\chi^2$ test with Yates' correction superior to Gastrografin enema in predicting a poor outcome ($P = 0{\cdot}004$ and 0·72, respectively) (*Tables 5* and *6*)

The incidence of diverticulitis diagnosed as severe by CT was statistically greater among men who were 50 years old or younger compared with other patients (men aged over 50 years and women) (44 *versus* 19 per cent, $P = 0{\cdot}04$), but the prognostic value of initial CT was still of statistical importance in men aged over 50 years and in women (*Table 7*).

## Discussion

Acute diverticulitis may be a serious condition; it occurs frequently and is poorly understood. Stress and diet in Western society are implicated in the formation of diverticula[1–5]. The process that leads to inflammation remains unclear. About two-thirds of patients with acute diverticulitis (78 per cent in the present series) have no history of previous intestinal disease[4,6,7]. Hôpital Cantonal Universitaire serves 600 000 people and admits about 40 patients with diverticulitis each year (seven patients per 100000 per year), a high rate similar to that found in other series[8].

Elective colectomy may be proposed after acute attacks of diverticulitis but there are no reliable signs to predict severe outcome. Elective colectomy may be resorted to more often because of its low mortality rate[9], which is lower than that for colectomies performed for complications[10]. No fatality occurred in 35 patients operated on electively in this series. Long-term results from this approach are promising[9,11].

Recurrence of diverticulitis occurs in 25 per cent of patients, usually within 2 years of the first attack[8,12,13]. The incidence may be lower because: (1) recurrence is not always clearly defined and occasionally includes patients who have not been completely cured; (2) large studies are retrospective; and (3) radiological confirmation is seldom obtained This probably explains the 7 per cent incidence of recurrence seen over a mean follow-up period of 24 months in this study. Most agree that recurrence is not more severe than first attacks and it responds favourably to conservative measures[8], in agreement with this study.

About a quarter of patients whose first attack is medically treated develop complications; 15 per cent of them require secondary operations[8,12–14], compared with 23 per cent in this series (25 of 107) Young patients seem particularly prone to complications[15–17] Common indications for delayed elective operations after a first attack include: (1) patients younger than 55 years; (2) patients whose first attack is particularly severe and who present acceptable anaesthetic risks, (3) patients with symptomatic and demonstrable complications such as fistulae, stenoses or residual abscesses; and (4) patients who suffer from a clear-cut, well defined recurrent diverticulitis[10,18–20].

In addition to its diagnostic value in patients with diverticulitis[21,22], CT is clearly superior to barium enema[22] and can be used in the percutaneous management of some abscesses[23]. Its prognostic value has not previously been recognized. Recurrences (clinically and radiologically proven) and symptomatic radiological findings such as continuing inflammatory processes, fistulae, stenoses and residual abscesses can be identified. In the present series, 24 of 107 patients who were treated conservatively for a first attack developed such complications. When assessing these complications against age, sex and initial CT and Gastrografin enema findings, it appears that: (1) men aged up to 50 years are significantly more prone to develop such complications; (2) the probability of developing a complication is significantly higher when the first CT revealed an abscess and/or extraluminal air and/or extraluminal Gastrografin; and (3) Gastrografin enema is not predictive of poor outcome. CT appears to be a good indicator to assess the severity of an attack of diverticulitis and to predict recurrence or other complications.

Elective colectomy may be advised after a first attack of acute left diverticulitis in men aged up to 50 years and/or in patients whose initial CT scan revealed the prognostic signs of severity described. In all other cases, continued conservative management remains justified.

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# *In vitro* modulation of haematoporphyrin derivative photodynamic therapy on colorectal carcinoma multicellular spheroids by verapamil

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*Photodynamic therapy has possible applications in the treatment of colorectal carcinoma. The photosensitizer haematoporphyrin derivative (HpD) is selectively retained by tumours. Agents which block p-glycoprotein, an export protein expressed to increased levels in a high proportion of colorectal carcinomas, may modulate photodynamic therapy by reducing HpD efflux from cells. Multicellular spheroids derived from the colorectal cell lines HRT18 and HT29 were incubated for 24 h with 1 μg ml*$^{-1}$ *HpD and 0, 1, 2 and 4 μM verapamil. Bioactivity demonstrated a dose-dependent potentiation of HpD-photodynamic therapy growth retardation. Clonogenic survival of cells disaggregated from spheroids treated with HpD-photodynamic therapy was reduced when spheroids were coincubated with verapamil. The mean(s.e.m.) efflux of HpD from spheroids into fresh medium assessed by fluorimetry was greater in spheroids treated with HpD alone (93·2(18·8) arbitrary units ml*$^{-1}$*) than in those treated with verapamil (18·1(2·8) arbitrary units ml*$^{-1}$*), P = 0·003. Flow cytometry demonstrated increased HpD fluorescence in cells derived from spheroids coincubated with verapamil over a range of HpD incubation concentrations. Verapamil can potentiate the bioactivity of HpD-photodynamic therapy and HpD may be a substrate for p-glycoprotein.*

Photodynamic therapy (PDT) is a new treatment being used in patients with a variety of malignant tumours[1]. It relies on selective uptake and retention of a photosensitizing agent, usually haematoporphyrin derivative (HpD), by tumours compared with surrounding normal tissues. Tumour necrosis is initiated by subsequent light irradiation. The process of cytotoxicity is complex and involves the production of toxic oxygen species, principally singlet oxygen[2]. Cytokines, including tumour necrosis factor, are released from activated macrophages[3] and photodynamic effects on the tumour microvasculature may contribute to the overall biological effect[4,5]. The vascular responses to PDT (vasoconstriction, platelet aggregation and thrombosis) are most likely mediated via the cyclo-oxygenase system[6,7] and result in ischaemic necrosis of tumour cells.

The relative contributions of direct tumour effects or secondary vascular mechanisms in PDT have been the subject of some debate[8]. Vascular shutdown may be the predominant mechanism for photodynamic damage following early intravenous photosensitizer administration[9]. Cowled and Forbes investigated whether vasoactive drugs could modulate the bioactivity of PDT[10]. Using Lewis lung carcinoma cells in a mouse tumour assay, noradrenaline, propranolol, hydralazine, and phenoxybenzamine either had no effect or inhibited the cytotoxicity of PDT. Verapamil, a calcium channel blocker and vasodilator, potentiated the action of PDT whereas other calcium channel blockers such as diltiazem and nifedipine had no effects, suggesting that the action of verapamil is not dependent upon its calcium channel blocking activity *In vitro* experiments using the same cell line did not show any potentiating activity by verapamil, leading to the conclusion that verapamil exerts its effect on the tumour vasculature.

Verapamil modulates the cytotoxicity of a variety of other chemotherapeutic agents such as doxorubicin and vincristine[11,12], probably through the competitive inhibition of a membrane-bound protein, p-glycoprotein[13]. This is a transport protein which has a very wide specificity and can actively export a range of substances, including antineoplastic agents, from within the cell[14]. It is expressed in many tissues in the human, particularly the adrenal gland and colon[15] Tumours arising from these tissues are generally intrinsically resistant to chemotherapy. Expression of p-glycoprotein in some tumours can be enhanced on exposure to certain chemotherapeutic agents[16], leading to the phenomenon known as multidrug resistance[17].

This study investigates the role of verapamil in the effects of PDT in an experimental model of colorectal carcinoma using multicellular tumour spheroids (MTS) of cells derived from the human colorectal cancer cell lines HRT18 and HT29. MTS are three-dimensional aggregates of cells grown *in vitro* and are considered to be similar in morphology to small nodular carcinomas before vascular invasion occurs[18]. They are especially useful for investigations where effects of tumour vasculature must be excluded. The response of MTS to PDT with HpD has been assessed[19,20], and is easily quantified[21].

## Materials and methods

### *Monolayer cultures*

Human colorectal cell lines HRT18 and HT29 (obtained from the National Tissue Type Collection, Public Health Laboratory Service, Porton Down, Salisbury, UK) were maintained in exponential growth using liquid overlay culture in 50-ml cell culture flasks (Falcon, Marathon Laboratory Supplies, London, UK) with RPMI culture

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medium (Gibco, Paisley, UK) supplemented with 15 per cent fetal calf serum, 50 $\mu$g ml$^{-1}$ benzyl penicillin, 50 $\mu$g ml$^{-1}$ gentamicin, 50 $\mu$g ml$^{-1}$ streptomycin, and 2·3 $\mu$g ml$^{-1}$ amphotericin B (Gibco) referred to as supplemented RPMI (SRPMI). Monolayers were subcultured after confluence using 0·01 per cent trypsin and 0·02 per cent ethylenediaminetetra-acetic acid (EDTA, BDH Chemicals Ltd., Poole, UK) in phosphate buffered saline. Cultures were tested periodically for mycoplasma and bacterial infections

*Production of spheroid cultures*

Culture vessels were base-coated with 1 per cent agar (Difco, Washington, USA) in RMPI to avoid cell adherence. Multicellular tumour spheroids were produced by seeding a single cell suspension (2 × $10^5$ cells) into base-coated tissue culture flasks which were agitated gently at 60 r.p.m After 5–6 days spheroids of suitable size (100–200 $\mu$m diameter) had usually formed which could be selected individually using a micropipette under a calibrated microscope.

*Preparation of HpD and verapamil*

HpD was made as described by Lipson *et al.*[22]. HpD from a single batch was used for all experiments described below. Verapamil hydrochloride was used as presented for clinical use (Abbot Laboratories Ltd., Queenborough, UK).

*Preincubation of MTS with HpD and verapamil*

Size-matched MTS (100–180 $\mu$m diameter) were transferred individually using a micropipette into wells of a 96-well plate for volume growth determinations or in groups of 20 into wells of a 20-well plate for experiments involving disaggregation and determination of cell survival, subsequent HpD extraction or flow cytometry. SRPMI containing HpD and concentrations of verapamil was then added to the wells containing MTS and incubation continued in the absence of light for 24 h. The MTS were then washed three times with drug-free SRPMI before further treatment.

*Light irradiation*

When required by the experiment the plates were exposed to light from four tungsten filament 'daylight' lamps (Luxram 15, 100 W, 'Daylight studios', London, UK) to produce light with a spectrum similar to that of daylight within the visible spectrum. Irradiance was measured using a photodiode radiometer (International Light IL 1700, Newburyport, Massachusetts, USA). The mean power density was 7·1 × $10^{-4}$ W cm$^{-2}$ in the range 300–1200 nm and irradiation was performed for the length of time required to deliver 4 J cm$^{-2}$ for each experiment (approximately 90 min) The temperature of the plates during light irradiation was in the range 28–32°C

*Measurement of the photodynamic effect*

The bioactivity of PDT was assessed by using both determinations of MTS volume growth[21] and the clonogenic survival assay[19]. The relative volume growth achieved at day 6 was the endpoint for statistical analysis using the Mann–Whitney *U* test.

*Measurements of HpD concentrations in MTS*

The relative amount of HpD within MTS and in the incubation medium was measured using two methods, fluorescence determination following extraction and hydrolysis of the HpD and direct cellular fluorescence determination using flow cytometry[19,23].

## Results

The cytotoxicity of HpD-PDT on HRT18 spheroids using HpD incubation concentrations of 0, 1, 2 and 4 $\mu$g ml$^{-1}$ with light irradiation is shown in *Figure 1*. Spheroids incubated with the same concentrations of HpD, but without light irradiation, showed no inhibition of growth (results not shown). The lower concentration of HpD was chosen to incubate spheroids for the bioactivity experiments with verapamil.

The addition of verapamil (0–4 $\mu$M) to 1 $\mu$g ml$^{-1}$ HpD caused a dose-dependent potentiation of growth inhibition of HRT18 MTS following light irradiation (*Figure 2*). A similar result was obtained using MTS derived from the cell line HT29 (*Figure 3*). This cell line divides more rapidly than HRT18 and appears to be more susceptible to growth inhibition by HpD-PDT[21].

These biological effects are dependent upon the activation of HpD by light since similar concentrations of HpD and verapamil, incubated without light irradiation, did not inhibit the growth of HRT18 MTS (*Figure 4*) and HT29 (results not shown). In addition light irradiation of HRT18 and HT29 MTS preincubated with verapamil in the absence of HpD had no effect on MTS growth (results not shown).

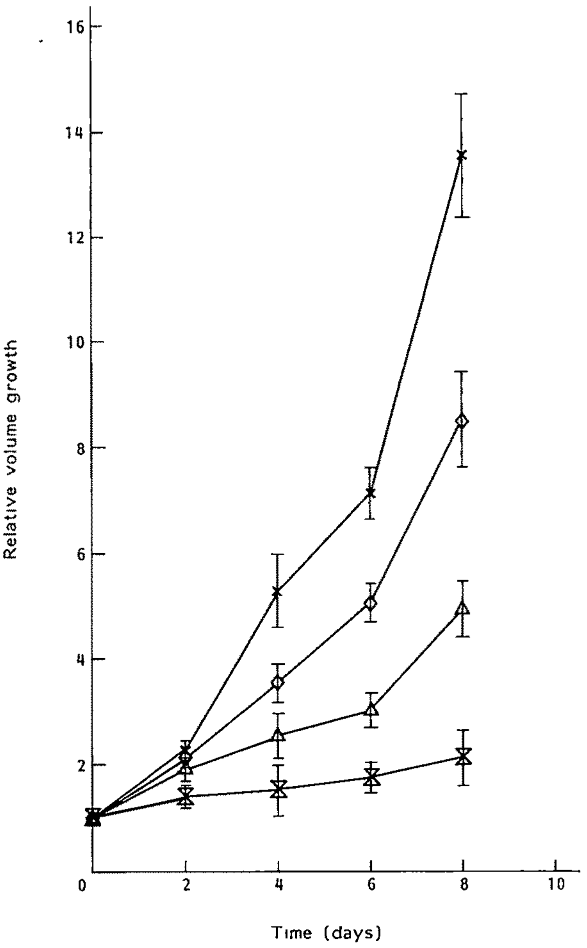

**Figure 1** *The inhibition of spheroid growth by haematoporphyrin derivative (HpD) and light (4 J cm$^{-2}$ polychromatic irradiation). HRT18 multicellular tumour spheroids were incubated in the presence or absence of HpD for 24 h. Values are mean(s.e.m.) of eight replicate spheroids. Results are from a single experiment representative of at least three separate experiments.* —×—, *HpD 0 $\mu$g ml$^{-1}$,* —◇—, *HpD 1 $\mu$g ml$^{-1}$;* —△—, *HpD 2 $\mu$g ml$^{-1}$,* ⧖, *HpD 4 $\mu$g ml$^{-1}$*

The results obtained using measurements of MTS volume growth were confirmed by measurements using the clonogenic cell assay. Cells disaggregated from HRT18 spheroids that had been treated with HpD (1 $\mu$g ml$^{-1}$) and light irradiation in the presence of verapamil (1 $\mu$M) produced fewer colonies than those incubated with HpD alone (*Figure 5*).

To explain the efficacy of verapamil in potentiating HpD-PDT, investigations on the uptake, retention and release of HpD by MTS were performed. *Figure 6* shows the relative amounts of HpD extracted from the cells of HRT18 MTS after preincubation with combinations of HpD (0–2 $\mu$g ml$^{-1}$) and verapamil (0–4 $\mu$M). Cellular concentrations of HpD are dependent on the external HpD concentrations but verapamil had no clear effect on cellular HpD concentrations.

Intracellular HpD fluorescence determined using flow cytometry demonstrated a direct correlation between extracellular HpD and relative intracellular HpD levels (results not shown) Increased HpD fluorescence in cells derived from spheroids was demonstrated in spheroids that were coincubated with verapamil in addition to HpD (*Figure 7*). In the absence of added HpD, verapamil had no effect on the basal fluorescence (*Figure 7*).

The efflux of HpD from MTS was determined by

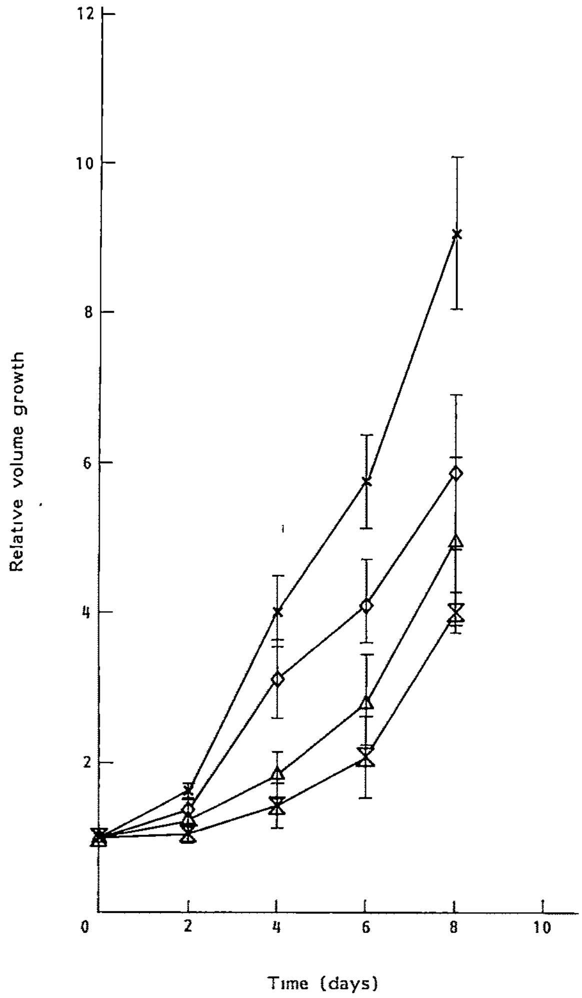

**Figure 2** *The effect of verapamil on the cytotoxicity of haematoporphyrin (1 μg ml⁻¹) and photodynamic therapy using HRT18 spheroids Values are mean(s.e m.) of eight replicate spheroids. Results are from a single experiment representative of at least three separate experiments.* —×—, *Verapamil 0 μM,* —◇—, *verapamil 1 μM,* —△—, *verapamil 2 μM,* —⧖—, *verapamil 4 μM*

preincubating groups of HRT18 MTS in medium containing either HpD or HpD and verapamil for 24 h. The medium was assayed for HpD by extraction, hydrolysis and fluorimetry. The results show significantly less HpD efflux from those MTS treated with HpD and verapamil than from those treated with HpD alone (*Figure 8*).

## Discussion

The present results demonstrate that verapamil potentiates the action of HpD-PDT in a non-vascularized *in vitro* model of colorectal carcinoma. These *in vitro* findings differ from those published previously[10] and may be the consequence of the relatively high HpD concentrations or different exposure conditions used. The exposure of monolayers to 25 μg ml⁻¹ HpD for 1 h would almost certainly have resulted in a maximal photodynamic cell kill in the experiments by Cowled and Forbes[10], allowing no margin for further enhancement by verapamil Certainly such maximal effects were approached with an HpD concentration of 4 μg ml⁻¹ for 24 h in the present experimental system using MTS.

As potential vascular actions of verapamil are excluded, an explanation for the observations could be that HpD-PDT might be subject to the verapamil-reversed multidrug resistance phenomenon that occurs with chemotherapeutic agents[11,12]. This would require that HpD is capable of acting as a substrate for p-glycoprotein and that intracellular levels of photochemically active HpD are reduced by this export process in those cells expressing the protein. In such cells verapamil, by inhibiting p-glycoprotein mediated HpD efflux, will lead to greater intracellular accumulations of HpD and to a potentially greater PDT effect on subsequent light activation.

HpD, as defined by Lipson *et al.*[22] and as used in these experiments, consists of a mixture of different porphyrin moieties. The composition is variable but consists of monomers, dihaematoporphyrin ether or esters and oligomers of up to eight covalently linked haematoporphyrin rings[24,25]. These compounds exhibit a strong tendency to self-associate in aqueous solution because of their planar conformation and hydrophobic nature[26,27].

When HpD has entered the cell the extent to which porphyrins aggregate is dependent on many chemical and physical factors of the cytosol. These include its ionic strength, pH and temperature[28]. The HpD concentration is particularly important; at the low HpD concentrations ( < 5 μg ml⁻¹) used in the spheroid experiments, HpD porphyrins exist predominantly in a disaggregated state Above this concentration aggregation by stacking predominates and proportionally less free porphyrin exists[29,30]. Within the cell these forms are in dynamic equilibrium and the dissociated forms of porphyrin are more easily taken up and released by cells[31]. The dissociated

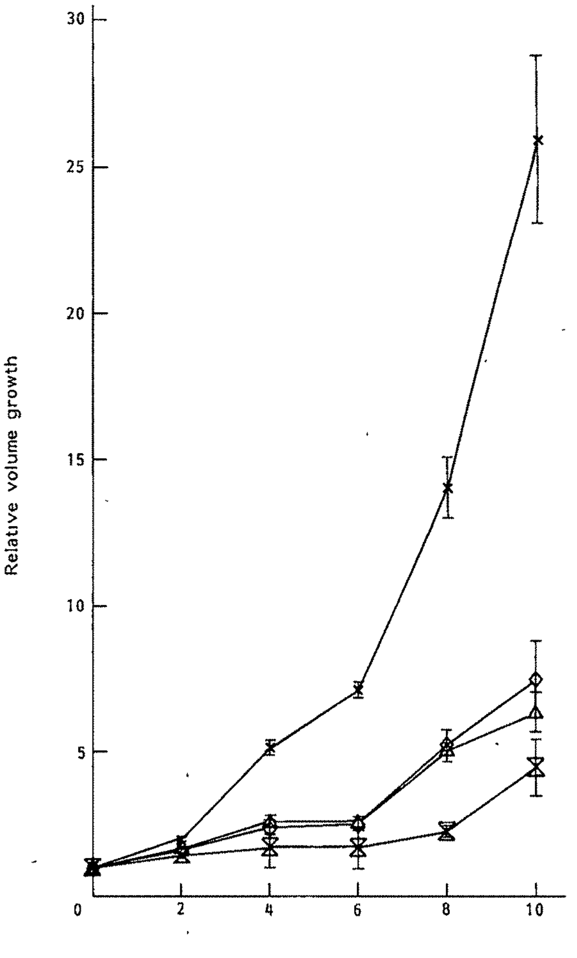

**Figure 3** *The effect of verapamil on the cytotoxicity of haematoporphyrin derivative (1 μg ml⁻¹) and photodynamic therapy using HT29 spheroids Values are mean(s e m.) Results are from a single experiment representative of at least three separate experiments* —×—, *Verapamil 0 μM,* —◇—, *verapamil 1 μM,* —△—, *verapamil 2 μM* —⧖—, *verapamil 4 μM*

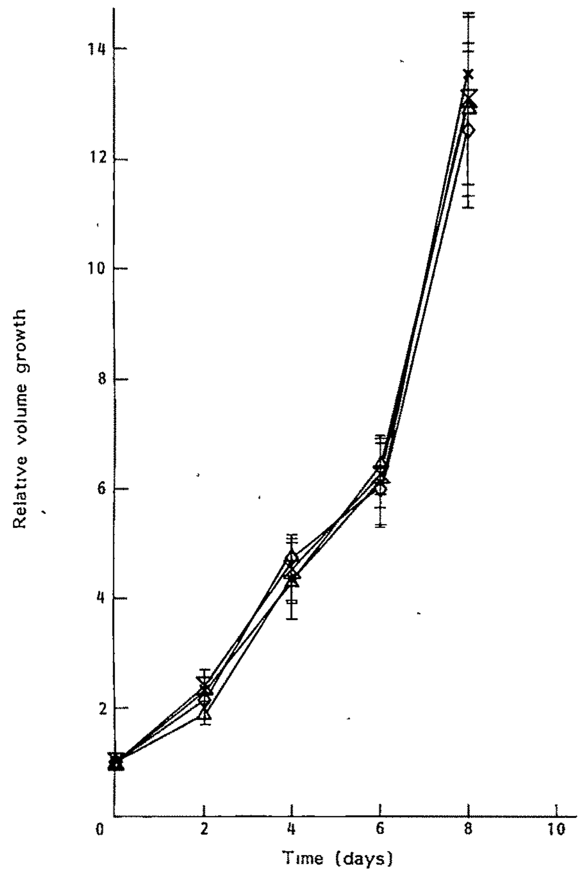

**Figure 4** *The effects of verapamil and haematoporphyrin derivative (1 μg ml⁻¹) on HRT18 spheroids growth in the absence of light. Values are mean(s.e m.). Results are from a single experiment representative of at least three separate experiments.* —×—, *Verapamil 0 μM;* —◇—, *verapamil 1 μM,* —△—, *verapamil 2 μM,* —⧖—, *verapamil 4 μM*

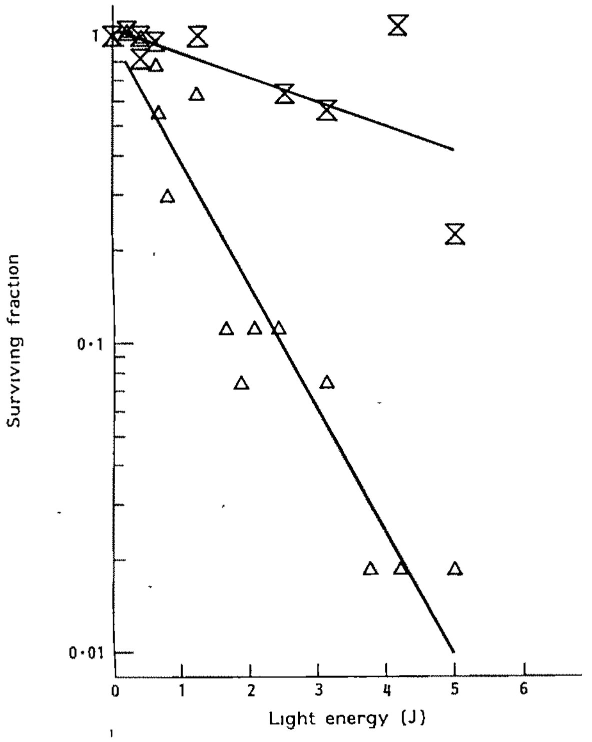

**Figure 5** *Clonogenic cell survival assay for disaggregated HRT18 spheroids. HRT18 spheroids, derived from a separate harvest to those used in* Figures 2 *and* 4, *were incubated with 1 μg ml⁻¹ haematoporphyrin derivative (HpD) alone or with a combination of 1 μg ml⁻¹ HpD and 1 μM verapamil for 24 h The graph shows the colony formation relative to that of the non-irradiated group* ⧖, *HpD control;* △, *HpD + verapamil*

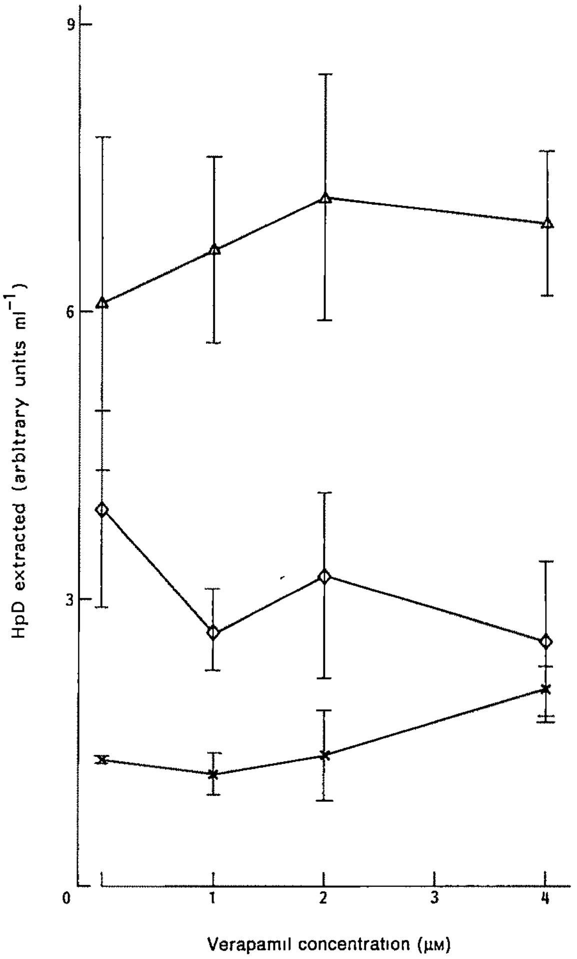

**Figure 6** *The effects of verapamil on the haematoporphyrin derivative (HpD) content of HRT18 spheroids measured by extraction and hydrolysis. Groups of 50 HRT18 spheroids were incubated with or without HpD in the presence or absence of verapamil (0–4 μM) for 24 h Values are mean(s.e.m ) of five separate experiments.* —×—, *HpD 0 μg ml⁻¹,* —◇—, *HpD 1 μg ml⁻¹;* —△—, *HpD 2 μg ml⁻¹*

forms of porphyrin contribute to the cellular fluorescence, since the aggregated HpD has a low fluorescence quantum yield[32]. This is of consequence in the interpretation of our results because flow cytometric determinations would only detect disaggregated HpD. The assay based on extraction and hydrolysis would detect the total amount of HpD within the cell.

The hypothesis that verapamil acts to block the efflux of HpD is supported by the direct measurements of HpD released from preloaded MTS (*Figure 8*). The addition of verapamil should therefore lead to greater accumulations of HpD within the cells. This was found using flow cytometry (*Figure 7*), but not when the extraction assay was used (*Figure 6*). Apart from the uncertainties caused by the limited sensitivity of this assay, this discrepancy could be a consequence of the different species of porphyrin detected by the two methods. Flow cytometry measures only the fluorescent fraction of HpD and hydrolysis and fluorimetry measures the total amount in terms of the monomeric form of HpD. Both techniques, therefore, are indirect measures of the photoactive fraction of HpD. Disaggregated HpD detected by flow cytometry was increased by verapamil but overall concentrations measured by hydrolysis and fluorimetry were barely affected. The disaggregated forms are believed to have the greater biological effect[33].

A major difficulty in interpreting the results of the HpD assays is their reliance on HpD fluorescence. This parameter is unlikely to detect the species of HpD that possess the greatest photodynamic activity. The transfer of absorbed light energy,

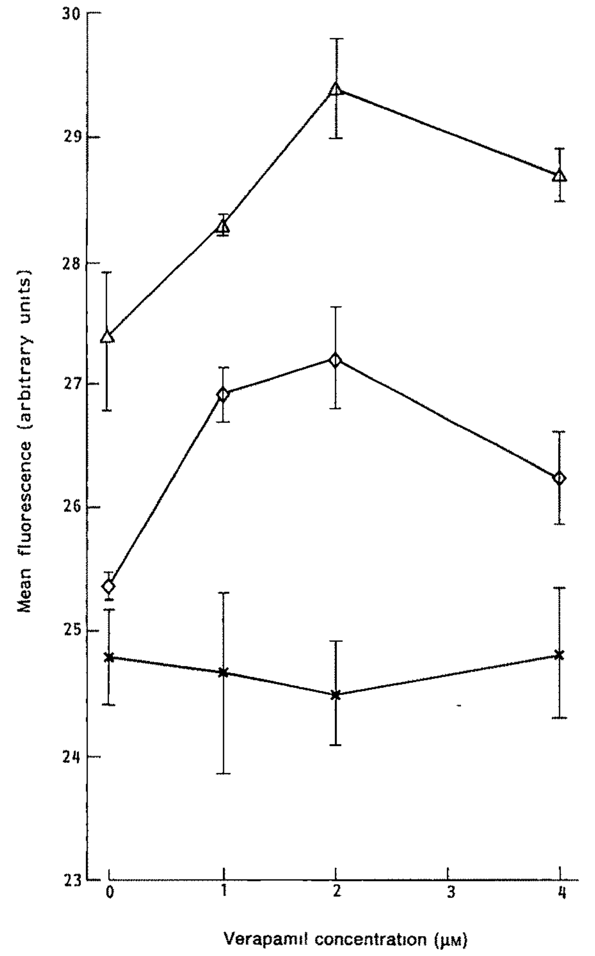

**Figure 7** *The effects of verapamil on the relative haematoporphyrin derivative (HpD) fluorescence of single cells derived from disaggregated HRT18 spheroids measured by flow cytometry HRT18 spheroids were incubated for 24 h in the presence or absence of HpD (0, 1 and 2 μg ml$^{-1}$) and with or without verapamil (0, 1, 2 and 4 μM). Values are mean(s e.m ) of the relative fluorescence in arbitrary units of cells from five separate experiments.* —×—, *HpD 0 μg ml$^{-1}$,* —◇—, *HpD 1 μg ml$^{-1}$;* —△—, *HpD 2 μg ml$^{-1}$*

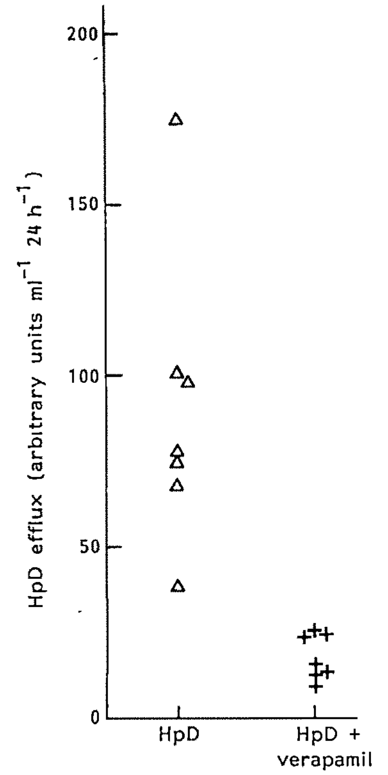

**Figure 8** *The effect of verapamil (2 μM) on the efflux of haematoporphyrin derivative (HpD) from HRT18 spheroids cultured in 1 μg ml$^{-1}$ HpD in the previous 24 h. The points represent the amount of HpD released into the culture medium over the subsequent 24 h from each group of multicellular tumour spheroids measured in arbitrary units ml$^{-1}$ 24 h$^{-1}$. The data represent the results of three separate experiments,* P = *0 003*

and as a consequence energy wastage in the form of fluorescence, is unlikely to identify the most efficient photosensitizers. This is important for two reasons: the fluorescent fraction of HpD is now considered to be less important for photodynamic activity resulting in cell injury and the fluorescent fraction as detected by both methods does not show a linear relationship with either the total or the photoactive fraction of HpD[33].

Verapamil could have effects other than a simple inhibition of efflux via p-glycoprotein to explain the observed potentiation of HpD-PDT. Verapamil might alter intracellular calcium concentrations so as to affect the equilibrium between associated and dissociated HpD, leading to a greater concentration of the latter. It may act directly on the porphyrin stacks as a surfactant, leading to dissociation as described by Jori *et al.*[34]. The experiments described here do not exclude such actions but do rule out any cytotoxicity or photocytotoxicity of verapamil in the absence of HpD (*Figure 4*). Inhibition of p-glycoprotein is the most likely mechanism for verapamil potentiation of HpD-PDT, but the mechanisms involved in HpD accumulation and release from cancer cells are not completely understood. The finding that verapamil can modulate these processes may have implications in the understanding of porphyrin photobiology and, if less toxic response modifiers than verapamil can be identified, in the treatment of patients with colorectal or other cancers.

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# Ileoanal pouch compliance and motor function

*Measurement of intrapouch pressure during continuous distension with water (pouchmetrography) was performed in ten patients with good pouch function after restorative proctocolectomy and a 'normal' baseline pressure curve was constructed from the mean pressures at 50-ml intervals. Eight other patients with poor pouch function were studied and the two groups were compared. Patients with poor function had significantly lower maximum tolerated volumes (297·5* versus *565 ml,* $P < 0·02$*) and volumes which caused urgency (135* versus *265 ml,* $P < 0·02$*). Baseline pressure curves were above the upper limit of the normal range (mean plus two standard deviations) for a substantial proportion of the recording in six of the patients with poor function. Large, isolated contraction waves were recorded in six of ten patients with good function and in three of those with poor function. Rhythmic waves were frequently seen in both groups but were more prominent in patients with poor function. Pouchmetrography is a provocative test of pouch motor function which may unmask abnormal muscle activity resulting from reduced compliance or a primary motility disorder.*

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Motor function of the ileoanal pouch is an important component of function after restorative proctocolectomy comprising both distensibility (compliance) and motility. The former accounts for changes in baseline intrapouch pressure, the latter for pressure rises above the baseline due to pouch contraction waves. There is a correlation between pouch compliance and function[1–7]. Compliance curves (or pouchmetrograms) of selected patients with good pouch function have been studied prospectively and contrasted with those from patients with symptoms and poor pouch function.

## Patients and methods

### *Pouchmetrogram technique*

A non-compliant, double-lumen catheter, 3 mm in diameter, with a compliant balloon (condom) fixed over the catheter tip was used. Water was infused through one channel at a rate of 50 ml per minute (peristaltic flow). The other channel was connected via a pressure transducer (Medex MX 848, Rossendale, UK) to a standard chart recorder (Devices® MX-4 73; Lectromed Ltd, Jersey, UK). The system was rendered air-free and emptied of water before insertion. The point at which the balloon was fixed to the catheter was positioned above the pouch–anal junction. Patients were studied in the left lateral position having first attempted to evacuate their pouch fully.

During filling, patients were asked to report the first sensation of filling (sensory threshold volume), the first urge to defaecate (urgency volume) and the point of maximum tolerated discomfort (maximum tolerated volume).

A compliance curve of the balloon in air was obtained before each patient study. True pouch pressure at any filling volume was calculated by subtracting the known pressure within the balloon (in air) at that volume from the pressure on the pouchmetrogram trace (balloon in pouch).

### *Patient groups*

*Good function.* Patients were selected prospectively for study on the basis of good clinical function. This was defined as five bowel actions or fewer per 24 h without medication, incontinence restricted to minor episodes of soiling no more than once per week, the ability to defer defaecation for more than 60 min and the ability to defaecate spontaneously. Ten patients (seven men, three women) aged 25–39 (median 32) years were studied 7–85 (median 22) months after ileostomy closure. Nine had W pouches and one had an S pouch.

*Poor function.* Eight patients with poor pouch function were referred for study. There were four women and four men aged 25–43 (median 35·5) years studied 7–78 (median 46·5) months after ileostomy closure. Four had W pouches and four had J pouches. Their clinical details are listed in *Table 1*.

### *Statistical analysis*

Results from the two groups were compared using the Mann–Whitney *U* test.

## Results

### *Pouch sensation*

The results are presented in *Table 2*. Urgency and maximum tolerated volumes were higher in patients with good function.

### *Baseline pressure curve*

Baseline pressure curves for the eight patients with poor function are shown in *Figure 1*. They are contrasted with the upper limit of normal, i.e. the mean pressure plus two standard deviations at 50-ml intervals from the ten patients with good function. Pressures up to 400 ml, the highest volume common to all ten patients, were included.

### *Pouch motility*

Superimposed upon the baseline pressure curve were three distinct waveforms.

Respiratory activity was characterized by low-amplitude (usually $<2$ cmH$_2$O) oscillations corresponding to respiration and abolished by breath-holding. It was seen in nine patients with good function and in three with poor function, but did not interfere with the interpretation of results.

Large isolated contraction waves (*Figure 2*) associated with the urge to defaecate were present in six patients with good function. They ranged from 8 to 36 cmH$_2$O in amplitude and lasted for 28–102 s. They first appeared at a median filling volume of 354 (range 139–495) ml and at a median baseline pressure of 6 (range 0–11) cmH$_2$O. In three patients the first appearance of an isolated contraction wave corresponded to the urgency volume.

Three patients with poor function displayed large isolated contraction waves. In two patients (B and G) the waves differed markedly from those seen in patients with good function, appearing at filling volumes of 15 and 50 ml and at baseline pressures of zero and 15 cmH$_2$O respectively, accompanied by

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**Table 1** *Clinical details of eight patients with poor pouch function*

| Patient | Details | Stool frequency (per 24 h) | Ability to defer defaecation (min) | Continence | Spontaneity of defaecation |
|---|---|---|---|---|---|
| A | J pouch<br>Chronic pouchitis | 6 | 60 | Frank faecal incontinence during sleep | Occasional straining only |
| B | J pouch | 15 (10–20) | 30 | Frank faecal incontinence during sleep | Occasional straining only |
| C | W pouch<br>Acute pouchitis | 10 (up to 20) | <15 | Soils daily | Strains frequently |
| D | J pouch | 10 (9–12) | 30 | Soils daily | Always spontaneous |
| E | W pouch | 10 | >60 | Occasional soiling only (less than once per week) | Always spontaneous |
| F | W pouch | 6–7 | 30 | Soils daily | Always strains. Often digitates. Poor pouch emptying on evacuation pouchography |
| G | W pouch | 10 | <30 | Occasional soiling only (less than once per week) | Always spontaneous |
| H | J pouch | 10 | <15 | Frank faecal incontinence during sleep | Always spontaneous |

**Table 2** *Pouch threshold volumes in patients with good and poor function*

| | Good function ($n = 10$) | Poor function ($n = 8$) | $P$* |
|---|---|---|---|
| Sensory threshold volume (ml) | 20 (15–65) | 30 (15–100) | n.s. |
| Urgency volume (ml) | 265 (125–505) | 135 (50–260) | <0·02 |
| Maximum tolerated volume (ml) | 565 (420–1065) | 297·5 (150–615) | <0·02 |

Values are median (range). *Mann–Whitney $U$ test; n.s., not significant

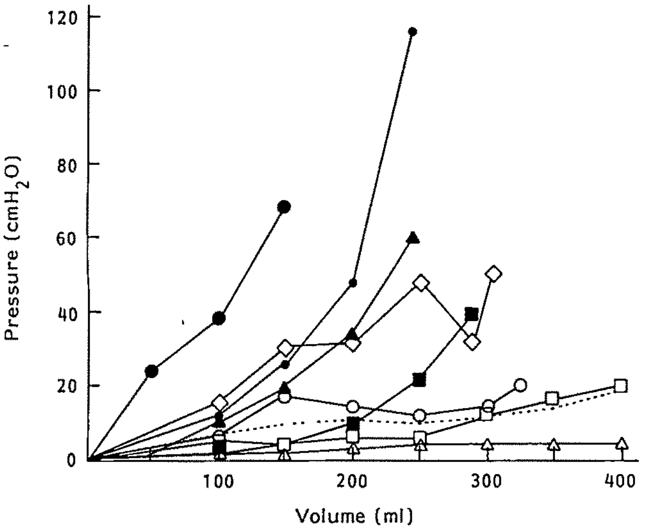

**Figure 1** *Baseline compliance curves (without super-added contractions) of the eight patients (A–H) with poor function plotted against the upper limit of 'normal' (· · · ·), derived from patients with good function •, Patient A; ◇, patient B, ■, patient C, ○, patient D; □, patient E, △, patient F, ▲, patient G; ●, patient H*

the first sensation of urgency They were 14–76 $cmH_2O$ in amplitude, lasted for 16–49 s, and were occasionally polyphasic (*Figure 3*).

Rhythmic waves (rhythmic pressure oscillations) occurring with a frequency of approximately 8/min were seen at some stage of the recording in eight patients with good function and in all eight patients with poor function. In those with good function they appeared fleetingly, usually as the maximum tolerated volume was reached, although they were occasionally superimposed upon isolated contraction waves. They did not exceed an amplitude of 10 $cmH_2O$ in this group. In patients with poor function, however, rhythmic waves were present for more of the duration of recording and were of higher amplitude (up to 34 $cmH_2O$) and frequency (8–12 *versus* 5–8/min) than in patients with good function (*Figure 4*).

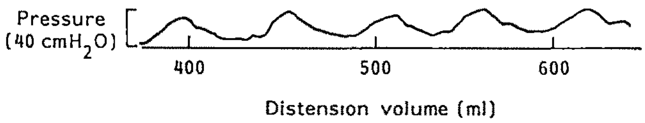

**Figure 2** *Segment of pouchmetrogram trace approaching maximum tolerated volume from a patient with good function. A sequence of typical, large, isolated contraction waves is demonstrated Note the steadily rising baseline pressure*

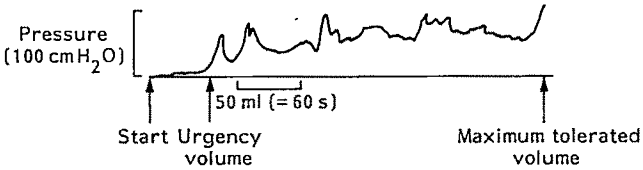

**Figure 3** *Complete pouchmetrogram of a patient with high stool frequency and incontinence showing early onset of high-amplitude, isolated contraction waves (patient B)*

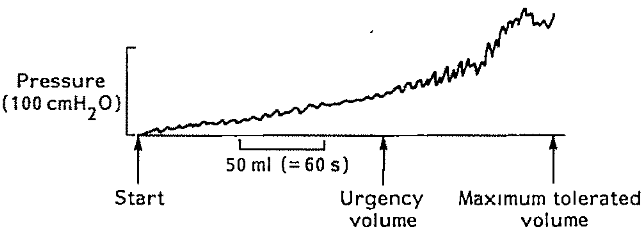

**Figure 4** *Prominent rhythmic activity (frequency up to 11 per min) in pouchmetrogram trace from a patient with poor function (patient A) Note the low maximum tolerated volume and high baseline pressures*

## Discussion

Pouchmetrography differs from other reported techniques of measuring pouch compliance in that water infusion occurs steadily rather than in intermittent boluses[1,5,8–14]. This abbreviates and standardizes the test and enhances reproducibility[15]. Continuous pressure recording, as distinct from intermittent recordings of the baseline pressure[6], reveals a motility profile superimposed upon baseline pressure changes.

The establishment of a range of baseline pressure changes for patients with good function, using pouchmetrography, has helped to identify clearly abnormal pouch motor function in patients with poor pouch function. The maximum tolerated volume was low and baseline pouch pressures were abnormally high for part or all of the compliance curve when compared with patients with good pouch function. The two patients with marked pouchitis (A and C) demonstrated grossly reduced compliance, and two other patients (B and G) demonstrated reduced compliance and abnormal contractile activity. This finding in patients with pouchitis is similar to that previously observed in the rectum of patients with ulcerative colitis[16].

These abnormalities may be due to diminished pouch distensibility, although it is not possible to exclude reduced pouch volume as a contributory factor. Decreased compliance and capacity both raise pouch pressure at any given filling volume and reduce maximum tolerated volume. The estimation of pouch compliance using the calculation $\Delta$volume/$\Delta$pressure (dV/dP)[2,7–10], usually taken at maximum tolerated volume, has therefore been omitted. The individual and the normal baseline pressure traces were not linear, as has previously been assumed[9,10] and dV/dP will therefore differ at different points of the pressure trace[17] Calculation of 'compliance' at the maximum tolerated volume will not be representative of the pouch over the distension spectrum

More sophisticated tests of intestinal distensibility, independent of changes in capacity, would be useful[18]. An electronic barostat[19] has been described to assess gastric compliance and motor function and could be usefully applied to the study of patients with an ileoanal reservoir.

The predominance of W pouches in the group with good function might be associated with a higher normal maximum tolerated volume than in patients with other pouch designs[20] Patients in this group were selected on the grounds of good clinical function and this is more closely related to increased pouch capacity[2,5–8,20,21] than to pouch design[7,22,23]. Motility patterns appear to be no different in the W pouches studied in this report from those in J, S and Koch pouches[9,11–14]. Comparison of pouchmetrograms from patients with a variety of pouch designs therefore appears valid.

The occurrence of isolated contractions and rhythmic wave patterns in ileal reservoirs is well documented[9,11–14]. In this study, isolated contraction waves appeared not to be triggered by the height of the baseline pouch pressure, which was often stable before their appearance and which returned close to prewave levels afterwards. They may occur more in response to a critical degree of pouch distension. Their absence did not preclude good function (four of ten patients), and they were seen in patients with good and poor function. Rhythmic waves were more obvious when the baseline pressure was higher but may not relate to pouch function. The precise origin and functional significance of these two waveforms is uncertain.

The pouchmetrogram characterizes compliance and the types of pouch motor activity in patients with good function In those patients complaining of poor function, reduced pouch compliance, primary disorders of pouch motility and the motility characteristics occurring in pouchitis are readily demonstrated

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# Influence of dietary calcium supplements on ileoanal pouch function and cytokinetics

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*A double-blind cross-over study was undertaken in 16 patients after panproctocolectomy and ileoanal pouch reconstruction to compare supplementary calcium (1·5 g/day) with placebo over 2 months with a 2-week washout period. Stool frequency was recorded and the effects on pouch mucosal crypt cellular proliferation were determined using an* in vitro *stathmokinetic technique which measures the crypt cell production rate (CCPR) and an immunohistochemical method using the Ki67 monoclonal antibody for proliferating nuclei. The median (interquartile range) diurnal stool frequency was reduced by calcium (4 (3–5) per day) compared with values obtained before treatment (7 (5–10) per day,* P < *0·002) and with placebo (7 (6–9) per day,* P = *0·002). Similarly, calcium reduced nocturnal stool frequency (1 (0–1) per night) compared with pretreatment and placebo (both 2 (1–3) per night,* P < *0·05) values. Calcium reduced the mean(s.e.m.) CCPR to 1·88(0·41) cells per crypt per hour compared with pretreatment (3·63(0·53),* P = *0·01) and placebo (3·24(0·43),* P = *0·002) values. Median (interquartile range) Ki67 activity was also reduced by calcium (13·2 (9·7–16·7) per cent), compared with values obtained before treatment (27·3 (14·3–30·2) per cent,* P = *0·001) and with placebo (26·0 (17·2–32·0) per cent,* P = *0·001). Stool frequency was significantly correlated with the CCPR (diurnal:* r = *0·37; nocturnal:* r = *0·31, both* P < *0·05). Nine patients used antidiarrhoeal medication while receiving placebo compared with four patients receiving calcium* (P = *0·032). This study has shown that supplementary oral calcium significantly reduced stool frequency in patients with pouches, a reduction that was associated with reduced cell proliferation. The mechanisms for this effect are not known.*

Until recently, proctocolectomy and end-ileostomy was the procedure of choice for surgical treatment of ulcerative proctocolitis and familial adenomatous polyposis. However, despite the remarkable improvements in stoma management, there is still a high psychological and social price to pay for an ileostomy[1,2]. The introduction of the ileoanal pouch procedure (restorative proctocolectomy) has changed the outlook of patients requiring operation for these disorders. More than 1000 of these procedures have now been carried out[3]. Ileal adaptation occurs after ileoanal pouch construction. The changes in ileal morphology after pouch formation include a chronic inflammatory cell infiltrate accompanied by intense villous atrophy, increased crypt depth and an increase in mucosal cell proliferation[4–7]. Frequency of defaecation after ileoanal pouch construction is directly correlated with the ileal crypt cell production rate (CCPR)[7], and hence factors that influence pouch ileal mucosal cell proliferation could modify its function.

Dietary calcium supplements have been shown to reduce crypt cell proliferation and to abolish the toxic effects of topical bile and fatty acids on colonic mucosa, either by sequestration or by a direct action on the colonic mucosa[8–13] Hence, dietary calcium supplements could exert a similar effect on ileal pouch mucosa.

We sought to test this hypothesis by undertaking a double-blind cross-over comparison of calcium with placebo. We recorded the effects on stool frequency and on crypt cell proliferation using monoclonal antibody Ki67 activity[14].

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*Paper based on an abstract presented to the January 1991 meeting of the Surgical Research Society*

## Patients and methods

### *Trial design*

Twenty patients who had undergone restorative panproctocolectomy with a pelvic ileal pouch at least 12 months previously were recruited All patients gave written consent to the study. Patients with pouchitis and those taking metronidazole or any antibiotic were excluded. The design was a double-blind cross-over study. Treatment was dispensed by the hospital pharmacy in coded form with precise instructions to each patient. Both the calcium and placebo were in powder form The dose of calcium was 1·5 g/day, given as calcium gluconate (BDH Pharmaceuticals, Atherstone, UK). The placebo was lactose powder, a substance known not to affect bowel habit in the absence of lactose intolerance, which was excluded by history; no Afro-Caribbean patients were included. The treatment period was 2 months on the first powder followed by a 2-week washout period before commencing the second powder for a further 2 months. The patients were specifically instructed to keep to their normal diet Nocturnal and diurnal stool frequency was recorded before the first treatment, after 2 months, and again after the second 2-month course The use of antidiarrhoeal medication was recorded and pouch biopsies were also obtained from the posterior wall of the pouch, 10 cm from the anal verge, after each treatment.

### *Crypt cell production rate*

Measurement of the CCPR was based on a previously described technique[15]. Biopsies were placed immediately into a circular Perspex dish (Falcon Plastics, Los Angeles, California, USA) containing RPMI 1640 (Gibco Laboratories, Paisley, UK) organ culture medium with added gentamicin (40 mg/ml), penicillin (100 units/ml) and fetal calf serum (1:9, vol/vol). The medium was equilibrated with 95 per cent oxygen and 5 per cent carbon dioxide at 37°C 1·h before use. The dish was placed into a sealed gas jar and kept at 37°C The same gas mixture was introduced into the sealed jar via the inlet valve for 10 min After 16 h, the medium was replaced with identical medium containing

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0·4 g/ml vincristine (Eli Lilly, Basingstoke, UK). Biopsies were removed 60, 120 and 180 min later, fixed in Carnoy's solution for 2–6 h and stored in 70 per cent ethanol

Following rehydration the specimen was hydrolysed in 1 M hydrochloric acid for 6 min at 60°C, stained with Schiff's reagent, and the slide was rinsed with 45 per cent acetic acid The mucosa was microdissected from each specimen and the number of arrested metaphase figures in ten crypts per specimen was counted This was undertaken by one person (D.Y.) on coded samples Linear regression analysis was used to determine the slope of metaphase accumulation, which was expressed as cells per crypt per hour.

*Ki67 immunohistochemistry*

Biopsies were immediately frozen in liquid nitrogen and stored at −40°C. Frozen specimens were cut 5 $\mu$m thick and fixed with acetate:ether (60 40, vol/vol) on albumin-coated slides. A three-stage peroxidase procedure was used[16], involving sequential 30-min incubations with the murine monoclonal antibody Ki67 and rabbit antimouse and swine antirabbit immunoglobulins (Dako, Copenhagen, Denmark) with intermediate washings of Tris-buffered saline with 40 per cent human serum The slides were developed with diaminobenzidine and hydrogen peroxide for 8 min and counterstained with haematoxylin. Negative controls were incubated with Tris-buffered saline before development. Activity was expressed as the percentage of positive cells to the total crypt cell population. This assay was performed by one individual (G H B ) on coded slides

*Ethical approval*

This was obtained from the ethical committee of the Central Birmingham Health Authority.

**Table 1** *Summary data on stool frequency, CCPR and Ki67 activity in patients before treatment and whilst receiving either calcium or placebo*

| | Before treatment | Calcium | Placebo |
|---|---|---|---|
| Stool frequency* ($n$) | | | |
| Day | 7 (5–10) | 4 (3–5) | 7 (6–9) |
| Night | 2 (1–3) | 1 (0–1) | 2 (1–3) |
| CCPR† | 3·63 | 1·88 | 3·24 |
| (cells per crypt per hour) | (0·53) | (0·41) | (0·43) |
| Ki67* (%) | 27·3 | 13·2 | 26·0 |
| | (14·3–30·2) | (9·7–16·7) | (17·2–32·0) |

Values are *median (interquartile range); †mean(s.e.m.). CCPR, crypt cell production rate

*Statistical analysis*

Any differences in the CCPR were determined by multiple slope analyses Multiple stool frequency and Ki67 activity data were compared by the Kruskal–Wallis test, if this was significant ($P < 0·05$) paired analysis was performed with the two-tailed Mann–Whitney $U$ test. Categorical data were analysed by Fisher's exact probability test (two-tailed). Correlations were performed using Pearson's formula (continuous data) and Spearman's rank correlation (categorical data). For correlations involving Ki67 and CCPR, normalization was undertaken by log transformation.

## Results

*Patients*

Fifteen patients complied fully with the trial protocol. Four patients did not comply with the study and were excluded. These patients stopped taking the powder for various reasons (holiday, inconvenient, forgot, changed mind) unrelated to any change in bowel habit. One patient wished to stay on the initial treatment (calcium gluconate); only pretreatment and postcalcium data are therefore shown for this patient. The median (range) age of the 16 patients who fully or partly complied with the study was 39 (17–64) years; nine (56 per cent) patients were female. The indications for surgery were ulcerative colitis ($n$ = 10), chronic idiopathic constipation ($n$ = 3), megacolon ($n$ = 2) and familial adenomatous polyposis ($n$ = 1). The median (range) time since the formation of the pouch was 22 (12–30) months.

*Presentation of data*

For simplicity, the data for each treatment period were grouped together and are summarized statistically in *Table 1*; individual values are given in *Figures 1–3*.

*Stool frequency* (Figure 1). Calcium treatment significantly reduced diurnal stool frequency compared with values obtained before treatment or with placebo (both $P$ = 0·002). Similarly, calcium reduced nocturnal stool frequency compared with pretreatment ($P$ = 0·005) and placebo ($P$ = 0·031) values. There was no difference in either instance when placebo and pretreatment values were compared. Nine patients used antidiarrhoeal medication while taking placebo, compared with only four receiving calcium treatment ($P$ = 0·032).

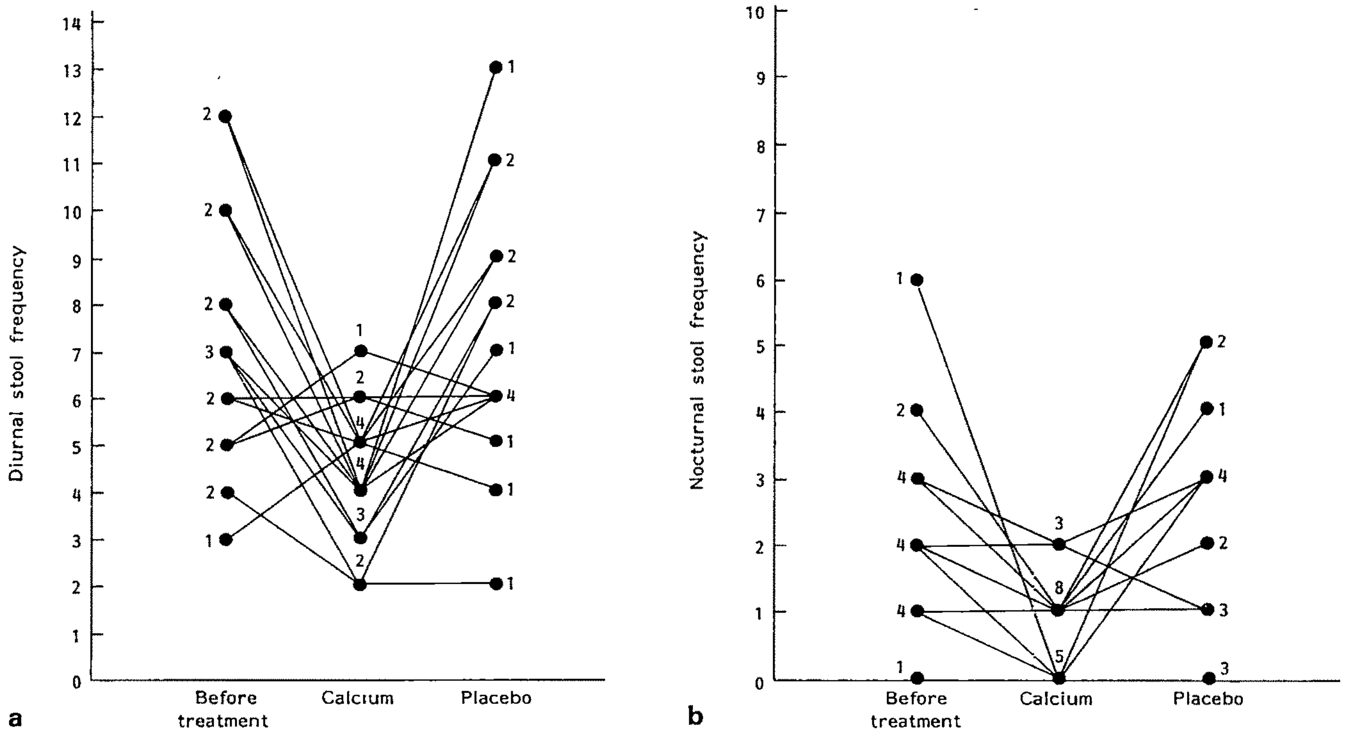

**Figure 1** a *Diurnal and* b *nocturnal stool frequency before treatment and during calcium and placebo treatment Numbers within the figures indicate the number of individuals with each stool frequency*

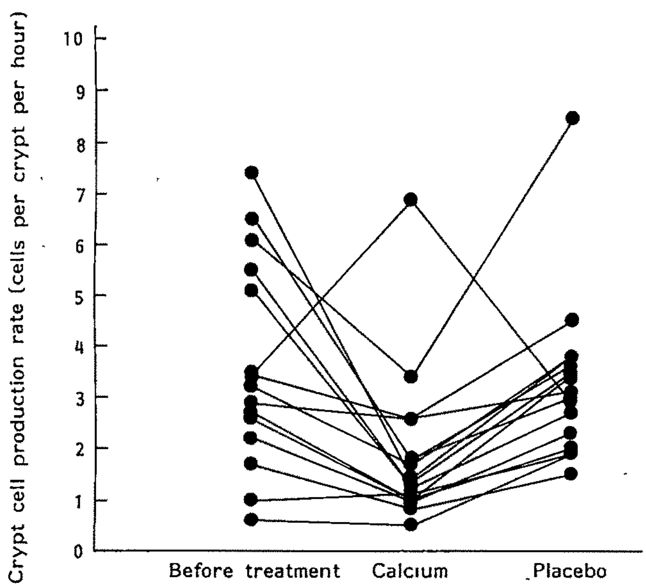

**Figure 2** *Crypt cell production rate before treatment and during calcium or placebo treatment*

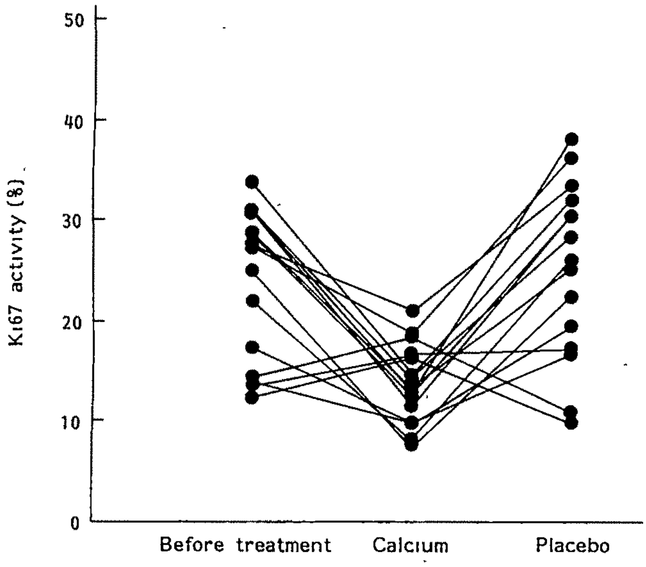

**Figure 3** *Ki67 cell proliferative activity before treatment and during calcium and placebo treatment*

*Crypt cell production rate* (Figure 2). The CCPR was significantly reduced by calcium compared with pretreatment ($P = 0{\cdot}01$) and placebo ($P = 0{\cdot}002$) values. There was no difference between placebo and pretreatment values.

*Ki67 activity* (Figure 3). Ki67 activity was significantly reduced by calcium treatment compared with pretreatment and placebo values (both $P = 0{\cdot}001$). There was no difference between placebo and pretreatment levels of Ki67.

*Correlations*

Diurnal stool frequency was significantly correlated with CCPR ($r = 0{\cdot}37$, $P < 0{\cdot}05$) and Ki67 activity ($r = 0{\cdot}52$, $P < 0{\cdot}001$). Similarly, nocturnal stool frequency was correlated with CCPR ($r = 0{\cdot}31$, $P < 0{\cdot}05$) and Ki67 activity ($r = 0{\cdot}43$, $P < 0{\cdot}01$). There were also significant correlations between diurnal and nocturnal stool frequency ($r = 0{\cdot}7$, $P < 0{\cdot}001$) and between CCPR and Ki67 activity ($r = 0{\cdot}58$, $P < 0{\cdot}001$).

## Discussion

Dietary calcium supplements in the dose used significantly reduced stool frequency in patients after ileoanal anastomosis with an ileal pouch. In agreement with previously published reports[8,9,11,17,18], this study also showed that supplementary calcium in double the normal daily intake reduced the ileal crypt cell production rate. The exact mechanism by which calcium exerts its effect on mucosal cellular proliferation has yet to be established. Newmark *et al.*[19] have proposed that the toxic (and also potentially tumour-promoting) effects of fatty acids and free bile acids on the colon may be inhibited by ionized calcium. Calcium supplements using several grams per day result in minimal variation of serum calcium in several long-term human studies[20–22], and an intake of 1·5 g/day has been recommended to prevent osteoporosis in postmenopausal women[23].

The troublesome diarrhoea seen in patients suffering from the short bowel syndrome and after jejunoileal bypass or ileostomy may be reduced by increased dietary calcium[24]. The 8-week duration of treatment with calcium or placebo in this study was chosen to ensure that exposure was long enough to exert an effect on intestinal cell kinetics, although the normal turnover time of ileal epithelial cells is only a few days and the proliferation pattern can change within 1 week of altering dietary intake[25]. Patients who had had a pouch reconstruction for at least 12 months were chosen because the CCPR increases for up to 6 months after surgery[7]. Patients with pouchitis were also excluded because of changes in the CCPR[26]. Lactose powder was chosen as a placebo because of the similar appearance, consistency and taste compared with calcium gluconate. Lactose does not affect bowel transit except in the presence of lactose intolerance. Although lactose intolerance was excluded by history, this may not have been absolutely reliable. The choice of placebo does seem appropriate, however, since the stool frequencies, CCPR and Ki67 activity were all very similar to the pretreatment values during treatment with placebo.

To date, only one human study[27] has failed to show any effect of calcium on cell renewal in the bowel. We have shown that supplementary oral calcium reduces the frequency of nocturnal and diurnal defaecation and that this is significantly associated with changes in cell proliferation using two different techniques, measurement of the CCPR[15] and Ki67 activity[16].

It remains to be determined whether the effects on cell proliferation in patients with pouches were secondary to reduced stool frequency or whether such effects were responsible for the beneficial clinical effects.

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133-135

# Congenital duodenal obstruction

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*Over the period 1980–1989, 49 patients with congenital duodenal obstruction due to duodenal atresia, duodenal stenosis or annular pancreas were treated. There were three deaths, all related to associated severe congenital anomalies and none related to surgery for duodenal obstruction; 78 per cent of the patients had associated congenital anomalies which, in some instances, complicated their management. Prenatal diagnosis by ultrasonography was made in 18 per cent of the patients and these patients had operations relatively earlier.*

Congenital duodenal obstruction is an uncommon but important clinical condition. Prematurity, associated anomalies, and nutrition pose significant problems in its management. In the recent past, a better understanding of the condition has evolved and there has been a continued improvement in its diagnosis and surgical management. From 1 January 1980 to 31 December 1989, 49 patients with congenital duodenal obstruction due to duodenal atresia, duodenal stenosis or annular pancreas were admitted to this hospital and these patients are reviewed. Patients having malrotation as the cause of duodenal obstruction were excluded from the series.

## Patients and methods

Forty-nine patients with congenital duodenal obstruction, 21 boys and 28 girls, were managed over the study period. The number of cases seen each year varied from one to eight (*Figure 1*)

The mean maternal age was 33 (range 15–44) years; 28 mothers were >30 years old and of these, 11 were >40 years old. The mean age of mothers who had babies with Down's syndrome was 34 years, whereas that of the mothers whose babies did not have this syndrome was 26 years; none of the latter was over 34 years old. Statistical analysis of the two groups of maternal ages was carried out using the Mann–Whitney *U* test and the difference was found to be statistically significant ($P < 0{\cdot}01$) The mean gestational age was 37 (range 31–40) weeks. Polyhydramnios had been present in 29 (59 per cent) pregnancies, undetermined in 16 and absent in four

Vomiting was the presenting symptom in 40 patients, in 32 of whom the vomitus was bile-stained. Associated congenital anomalies were detected by physical examination, radiography and echocardiography. An erect abdominal radiograph was performed in all cases. In 45 (92 per cent) patients the radiograph revealed a double bubble sign Gastric dilatation was seen in 32 cases and air in the distal bowel in six Because there was some doubt regarding the precise diagnosis, 16 patients underwent upper gastrointestinal tract contrast radiography; nine were shown to have incomplete and seven complete duodenal obstruction Fourteen patients underwent prenatal ultrasonography for maternal polyhydramnios and a diagnosis of duodenal atresia had been made in nine of these; these were patients in whom a nasogastric tube was passed immediately after birth and who did not, therefore, present with vomiting.

The mean age at onset of symptoms was 1·3 days The mean age at admission was 3·6 days (1·2 days with prenatal diagnosis and 4 1 days with postnatal diagnosis). This excludes one patient who presented at the age of 6 years Initial management included passage of a nasogastric tube, intravenous fluid therapy and care of the respiratory tract, including intubation and ventilation if necessary. Appropriate consultants were involved in the management of any associated anomalies discovered

The mean age at operation was 6 6 (range 1–48) days, excluding the patient at 6 years The mean age at operation of patients with prenatal diagnosis was 2 6 days compared with 7·5 days for patients whose diagnosis had been made after birth

The operative findings included a duodenal web in 15 patients (complete in five and incomplete in ten), three of whom had windsock anomaly. There was a complete duodenal gap in 29 patients, three patients had two blind ends of the duodenum connected by a fibrous cord (type 2 atresia) and one had duodenal stenosis. Eighteen patients had annular pancreas: in 12 the annular pancreas was associated with a complete gap, in four with a web, in one with duodenal stenosis and one patient had annular pancreas as the only anomaly. Proximal duodenal dilatation was seen in 26 patients Nine patients had accompanying malrotation, which was found with a complete gap in five, with a complete gap and annular pancreas in two and with an incomplete web in two. None of the patients had accompanying distal small bowel atresia.

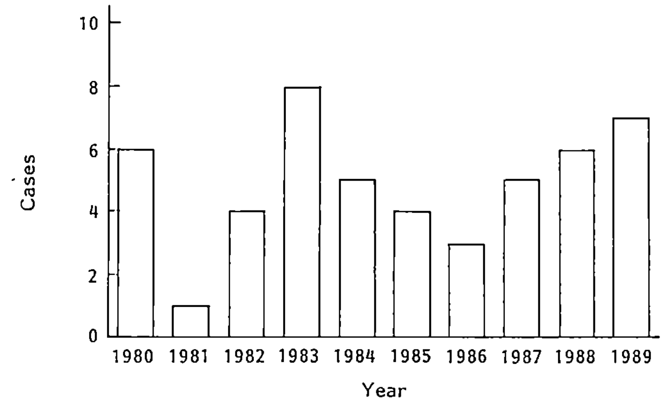

**Figure 1** *Number of cases per year of congenital duodenal obstruction (atresia, stenosis, annular pancreas)*

Duodenoduodenostomy was performed in 46 patients, 41 underwent side-to-side duodenoduodenostomy and five underwent the diamond shaped duodenoduodenostomy originally described by Kimura *et al* [1]. In the remaining patients, duodenojejunostomy (one), incision of the web (one) and excision of the web (one) was performed. A single layer non-absorbable suture was used in most instances A transanastomotic jejunal feeding tube was placed in 47 patients, a nasogastric tube in 45 cases and gastrostomy tube in four infants The decision about which technique to use was made by the operating surgeon at the time of repair

## Results

There were 38 patients with associated anomalies (*Table 1*) Of these, 34 (69 per cent of the 49) had Down's syndrome; five had Down's syndrome only, 16 had Down's syndrome with one other anomaly, nine had Down's syndrome with two other anomalies and four patients had this syndrome with multiple anomalies The final four patients had a single isolated anomaly other than Down's syndrome

After operation transanastomotic tube feeding was commenced at a mean of 3·2 (range 1–6) days. The mean time for starting oral feeding in patients with a transanastomotic tube was 13·4 (range 4–39) days. Two patients who did not have transanastomotic tubes were commenced on oral feeding at 5 and 6 days respectively. Total parenteral nutrition was used in 18 cases Patients undergoing a diamond shaped duodenoduodenostomy started oral feeding on average 3·7 days earlier than those with a side-to-side duodenoduodenostomy and 4 4 days earlier than the infant who underwent duodenojejunostomy.

There were no anastomotic complications. Two patients developed late small bowel obstruction secondary to adhesions which required laparotomy. One patient with a gastrostomy

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**Table 1** *Congenital abnormalities associated with duodenal obstruction*

| Anomalies | *n* |
|---|---|
| Down's syndrome | 5 |
| Down's syndrome, VSD | 6 |
| Down's syndrome, complete atrioventricular canal defect | 4 |
| Down's syndrome, PDA | 2 |
| Down's syndrome, ASD | 1 |
| Down's syndrome, Fallot's tetralogy | 1 |
| Down's syndrome, malrotation | 1 |
| Down's syndrome, Hirschsprung's disease | 1 |
| Down's syndrome, VSD, ASD | 2 |
| Down's syndrome, VSD, PDA | 2 |
| Down's syndrome, VSD, cleft palate | 1 |
| Down's syndrome, PDA, talipes equinovarus | 1 |
| Down's syndrome, Meckel's diverticulum, malrotation | 1 |
| Down's syndrome, UDT, malrotation | 2 |
| Down's syndrome, VSD, PDA, nystagmus | 1 |
| Down's syndrome, VSD, left cystic kidney, left PUJ obstruction, malrotation | 1 |
| Down's syndrome, VSD, ASD, UDT, malrotation | 1 |
| Down's syndrome, VSD, PA, imperforate anus, ambiguous genitalia, syndactyly, rigid interpharyngeal joints | 1 |
| Malrotation | 3 |
| Meckel's diverticulum | 1 |

VSD, ventriculoseptal defect, PDA, patent ductus arteriosus; ASD, atrioseptal defect; UDT, undescended testis, PUJ, pelviureteric junction; PA, pulmonary atresia

**Table 2** *Mortality in three infants*

| | Patient no | Details of mortality |
|---|---|---|
| Early | 1 | Pulmonary atresia, VSD, imperforate anus, rectovesical fistula, ambiguous genitalia, syndactyly Died at 4 days |
| Late | 2 | Birth asphyxia, VSD, CCF and pneumonia. Died at 4 months |
| | 3 | VSD, ASD, CCF Died at 8 months |

VSD, ventriculoseptal defect; CCF, congestive cardiac failure, ASD, atrioseptal defect

tube had inflammation around the tube and one developed a wound infection Other complications included congestive cardiac failure (nine patients), pneumonia (five patients), necrotizing enterocolitis (one patient) and lactose intolerance (two patients)

The mean hospital stay of patients undergoing a diamond shaped duodenostomy was 9·4 days shorter than those with a side-to-side duodenostomy Of the 49 patients 46 survived. The three deaths occurred in infants with severe associated anomalies including congenital heart defects (*Table 2*). All deaths occurred in the first 5 years of the series

The mean follow-up of 45 patients was 19·4 months. One patient has been lost to follow-up but those patients followed up had a normal duodenal status at last review.

## Discussion

Of the 49 patients undergoing surgery for duodenal obstruction 46 survived; the three deaths occurred because of severe anomalies and were unrelated to operation. Hence, from the point of view of operation for duodenal obstruction, the survival rate in this series was 100 per cent. This compares well with the series of Mooney *et al.*[2] and favourably with other series in which the survival rate ranged from 42·5 to 67 per cent[3–6] It is worthy of note that the male to female ratio of 21:28 in the present series contrasts with 6:14 reported by Mooney *et al.*[2].

The incidence of Down's syndrome (69 per cent) was much higher than in other published reports[4,7,8]. This can be explained by the high proportion of older mothers in the present series There was a statistically significant difference in the mean age of the mothers of infants with and without Down's syndrome. For the same reason, the rate of associated anomalies (78 per cent) was also higher than in other reports[2,4,9].

There was a delay between the onset of symptoms (1·3 days on average) and operation (6·6 days on average), which was caused by a combination of late referral (mean 3·6 days), need to confirm the diagnosis, correction of fluid and electrolyte abnormalities, and assessment and management of associated anomalies. The patients in whom prenatal diagnosis had been made were operated on relatively earlier. Nowadays, many mothers undergo prenatal ultrasonography and we anticipate that the prenatal diagnosis of duodenal obstruction will increase. Particular care should be exercised with mothers who are over 35 years of age.

At operation, three patients were found to have the windsock anomaly, which is a variation of the intact membrane (type 1 atresia) and is caused by peristalsis and high proximal intraluminal pressure. The membrane protrudes distally into the duodenum and consequently the actual level of obstruction may be several centimetres distal to the point of origin of the membrane Various operative techniques have been used in the past for the treatment of congenital duodenal obstruction, including duodenoduodenostomy and duodenojejunostomy and excision or incision of a web Duodenoduodenostomy is considered to be a more physiological procedure than duodenojejunostomy[9] In 1977 Kimura *et al.*[1] described the technique of the diamond shaped anastomosis which was used in five patients in the present series. As in other series[9], these patients had earlier oral feeding than those with a side-to-side duodenoduodenostomy. Because of the intimate proximity of the ampulla of Vater to the actual obstructing lesion in many cases[10], duodenoduodenostomy is our preferred procedure rather than the direct excision of the duodenal membrane.

Contrary to the experience of others, there were no complications as a consequence of the transanastomotic tube, which we attribute to the use of a soft Silastic® tube (Silicone Paediatric Duodenal Tube; Vygon, Ecouen, France). However, the period between operation and commencement of oral feeding was prolonged in patients with a transanastomotic tube compared with that in patients without such a tube, both in this series and others[2]. We now concur with the trend not to use transanastomotic tubes and to commence oral feeding earlier. We also recommend more frequent use of the Kimura technique.

Gastrostomy tubes (in four patients) were placed in the first half of the series. With the exception of patients with additional congenital abnormalities such as oesophageal atresia, gastrostomy tubes are no longer placed. Thus the complications of gastrostomy and the possible need for an additional surgical procedure, for closure of the occasional persistent gastrocutaneous fistula following removal of the tube, are avoided.

It can be appreciated from several different series, as well as by comparing the first half of the present series with the second half, that mortality and morbidity rates are improving with the passage of time In the authors' view, the excellent survival figures reflect the advances in intensive and perioperative neonatal surgical care of the past decade; these include nutritional support and better management of respiratory problems.

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# Announcement

## International Hepato-Biliary-Pancreatic Association Frank Glenn Travelling Fellowship 1992

The International Hepato-Biliary-Pancreatic Association invites applications for the above travelling Fellowship. A stipend of SFr 5000 is available to subsidize a young investigator in the field of hepatobiliary and pancreatic disorders. The applicant must be sponsored by a member of the Association. The stipend may be used to support a laboratory project and/or to subsidize travel expenses which are deemed appropriate to the field of investigation. Applicants must be under 40 years of age and should have an established record of at least one or several papers concerning liver, biliary or pancreatic disease.

Applications should be made in writing and should include the following:

1. a copy of the applicant's curriculum vitae;
2. a summary of 1–2 pages of a research protocol describing how the stipend is to be used;
3. a letter of nomination from a member of the IHBP Association or your Department Chairman.

Applications should be sent to: Dr Haile T. Debas, University of California, San Francisco, Department of Surgery, San Francisco, CA 94143-0104, USA by 30 April 1992. Telephone: (415) 476-1236. Facsimile: (415) 476-1734.

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# Accurate method to measure the percentage hepatic replacement by tumour and its use in prognosis of patients with advanced colorectal cancer

*The natural history of patients with colorectal hepatic metastases was studied following resection of the primary tumour. Patients were stratified according to the presence of extrahepatic disease and the percentage hepatic replacement (PHR) measured by planimetry of computed tomographic images. The median(semi-interquartile range (s.i.r.)) PHR of patients without extrahepatic disease was 15·0(10·5) and for those with extrahepatic disease 5·4(2·2)* ($P < 0{\cdot}02$)*. The median(s.i.r.) PHR of all patients was 8·7(8·5). The median(s.i.r.) survival of all patients was 125(85·5) days, 92(114) days for patients with extrahepatic disease and 175(133·5) days for patients with disease confined to the liver* ($P < 0{\cdot}02$)*. A linear correlation between the natural logarithm of PHR and survival was demonstrated* ($\rho = -0{\cdot}76$, $P < 0{\cdot}001$) *for patients without extrahepatic disease. Extrahepatic disease in patients with colorectal hepatic metastases is a major determinant of survival; PHR has a direct association when extrahepatic disease is absent.*

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The extent of tumour within the liver is an important factor in assessment and prognosis of patients with colorectal carcinoma[1]. Previous assessment uses terms such as solitary, multiple in one lobe and multiple in both lobes[2]; percentage hepatic replacement (PHR) is a potentially more sensitive measure of tumour extent and is being applied for assessment and staging of patients[3]. PHR can be assessed at laparotomy[4] and using a variety of imaging techniques such as hepatic scintigraphy[5], angiography[6], computed tomography (CT) and ultrasonography[4]. CT is likely to be the most accurate[4], but all methods rely on subjective interpretation and PHR estimates are usually approximated into stages comprising increments of 25 per cent or more[4]. Such estimates may be inaccurate and insensitive. A system to quantify PHR accurately would provide objective assessment of treatment and may give useful prognostic information for patient management.

A microcomputer-based system which utilizes a quantitative method to measure PHR from CT images has been devised. This study investigates the relationship between PHR by this system, the presence of extrahepatic disease and survival in a retrospective series of patients with colorectal liver metastases.

## Patients and methods

### *Hepatic imaging*

The liver was imaged by CT using a Phillips tomoscan 350 (Phillips, Eindhoven, Holland). Contiguous hepatic images were obtained with a straight gantry angle and a slice thickness of 0·9–1·8 cm. Contrast enhancement was performed for all patients.

### *Measurement of percentage hepatic replacement*

PHR was measured using the technique of planimetry: a digitizing tablet and mouse (TDS LC series II, Terminal Display Systems Ltd, Blackburn, UK) was used to plot a series of points on the perimeters of liver and metastases from images obtained by CT. A personal computer was used to calculate the cross-sectional areas of liver (L) and metastases (M) for each sequential slice of the scan. The slice thickness remained constant for all CT scans so that PHR could be calculated using the formula:

$$\mathrm{PHR} = \frac{\sum \mathrm{M}}{\sum \mathrm{L}} \times 100$$

### *Accuracy of planimetry*

The accuracy of planimetry was assessed using PHR values obtained from excised cadaver livers containing metastases ($n = 5$). The PHR value was compared with that after fine dissection of the liver into metastatic tissue and normal liver parenchyma. The volumes of these two components were measured using water displacement and the PHR calculated from these values. The accuracy of planimetry ranged from −3·3 to −1·3 per cent (percentage errors), greater accuracy occurred when planimetry was peformed on livers with larger PHRs. The coefficient of variation of values obtained from repeated measures of planimetry PHR varied from 3·57 to 0·9. These performance parameters are comparable to other studies which have investigated the accuracy of planimetry for volume estimations[7,8].

### *Patients*

The records of all whole body CT scans performed at the Royal London Hospital were reviewed, from installation of the scanner in 1984 to 31 December 1989. From these records 36 scans were obtained from patients in whom colorectal liver metastases had been imaged and for whom adequate clinical details could be obtained from case notes, hospice records and correspondence with the general practitioner. The patients (median age 71, range 62–85 years) had undergone resection of primary colonic tumours and had received no further treatment. CT had been performed shortly before surgery or in the postoperative period. Of these patients 13 had extrahepatic disease which was not resected at the time of laparotomy, or developed clinical or radiological evidence of tumour outside the liver following apparently curative surgery; 23 patients had no clinical or radiological evidence of extrahepatic disease at subsequent follow-up. Survival was determined in days from the date of the CT scan.

### *Statistical analysis*

Data on survival, extrahepatic disease and PHR were analysed using the BMDP statistical package (BMDP Statistical Software, Los Angeles, California, USA). Data are presented as medians and semi-interquartile ranges (s.i.r.) because of non-normal distributions

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Survival was compared with the Cox–Mantell two-group non-parametric test designed to test survival curves with exponential functions. Differences in PHR were assessed using the Mann–Whitney *U* test.

## Results

All patients with metastases imaged by CT during the study period died as a result of their disease. Data on their survival and the planimetry PHR are summarized in *Table 1*. A Kaplan–Meier survival plot demonstrated an exponential relationship between actuarial survival and time for both groups (*Figure 1*). The difference between these two groups was significant ($P < 0{\cdot}02$, Cox–Mantell statistic). The natural logarithm of PHR demonstrated a linear correlation with survival time for those patients with no extrahepatic disease (*Figure 2*). The correlation coefficient between these parameters was $-0{\cdot}76$ ($P < 0{\cdot}001$) For those patients with extrahepatic disease the correlation between these parameters was not statistically significant ($\rho = -0{\cdot}23$, data not shown).

**Table 1** *Percentage hepatic replacement and survival of patients with colorectal liver metastases imaged using computed tomography*

| Group | Median(s.i r.) percentage hepatic replacement | Median(s.i.r.) survival (days) |
|---|---|---|
| All patients ($n = 36$) | 8·7(8·5) | 125(85·5) |
| Patients with extrahepatic disease ($n = 13$) | 5·4(2·2) | 92(114) |
| Patients without extrahepatic disease ($n = 23$) | 15(10·5) | 175(133·5) |

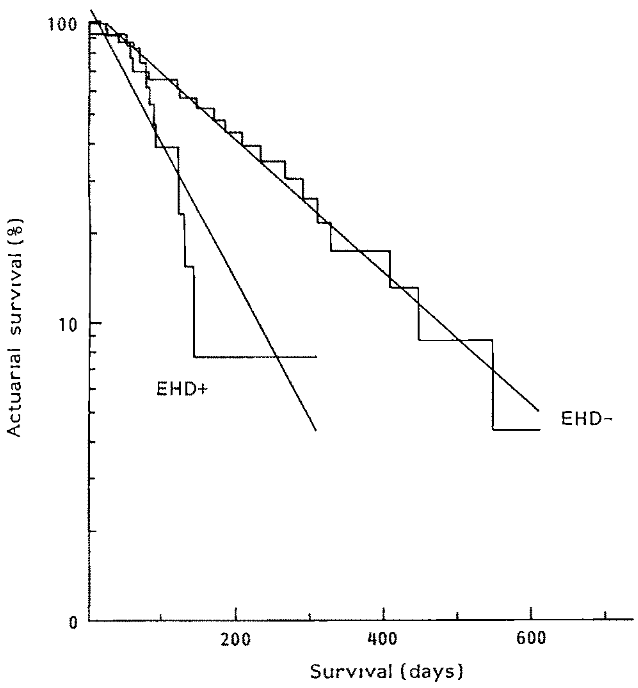

**Figure 1** *Kaplan–Meier survival plots for patients with colorectal hepatic metastases comparing patients with evidence of extrahepatic disease (EHD+) and those without (EHD−) A logarithmic actuarial survival axis is used and the exponential regression line for both sets of patients plotted*

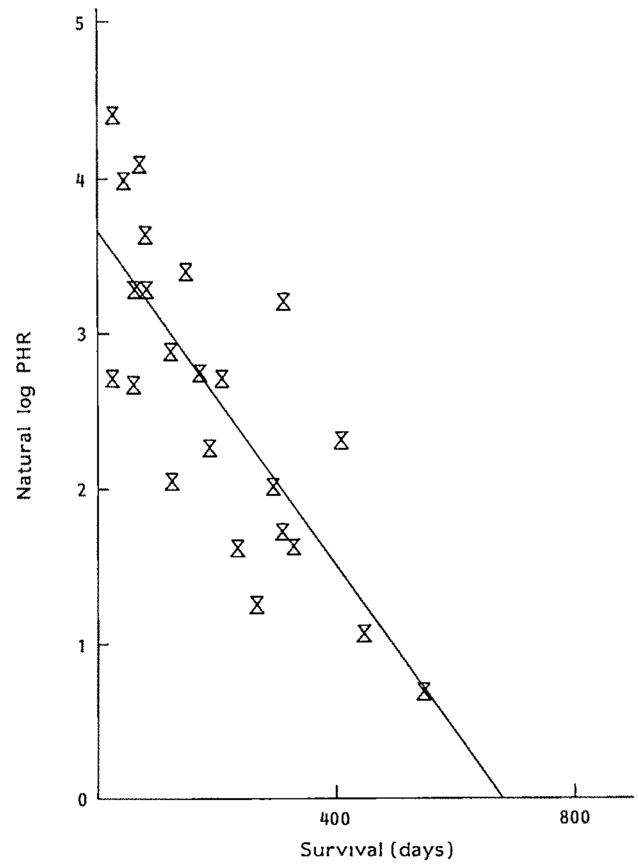

**Figure 2** *A plot of percentage hepatic replacement (PHR) as determined by planimetry and the survival of patients in days from computed tomographic examination of the liver for patients without extrahepatic disease* ($\rho = -0{\cdot}76$, $P < 0{\cdot}001$)

## Discussion

The presence of liver metastases in a patient with colorectal carcinoma carries a poor prognosis with average survival in the order of 6 months[9]. There are several factors which influence the overall prognosis but it is apparent that the extent of secondary spread within the liver is important[10]. Mansfield *et al.*[11] introduced the concept of PHR which has superseded descriptive assessments of tumour extent as the basis of many staging criteria presently used to stratify patients[12]. A PHR estimation therefore has prognostic importance and, because liver size varies proportionally with body surface area[13], provides an assessment of host tumour burden that can be applied to all patients irrespective of body mass and liver size The technique of planimetry is one method of measuring PHR accurately.

The present study makes the assumption that these patients are a representative sample of patients with metastases diagnosed by other means. The survival of patients who had extrahepatic disease was significantly worse than those without extrahepatic disease. A comparison of PHR for these two groups showed that patients with extrahepatic disease had less disease within the liver, indicating that the presence of extrahepatic disease is particularly detrimental for survival A linear correlation between the natural logarithm of PHR and survival was noticed for patients without extrahepatic disease.

Comparisons of equidistant points on a natural log percentage axis represent equivalent relative differences that can be applied throughout the whole range of PHR, in contrast to a linear PHR scale[14]. The relationship between these parameters indicates that for those patients without extra-hepatic disease the extent of tumour within the liver has a direct association with the duration of survival. This observation could be useful for prognosis. The survival advantage of patients with low PHR values may be related to the functional reserve of the liver. Liver metastases may not grow in a predetermined way, however, as might be interpreted from the linear association between PHR and survival. This would require confirmation in a prospective study on patients with repeated CT scans of metastases.

The natural history of patients with liver metastases is determined by the presence of extrahepatic disease. PHR is of particular prognostic significance when metastatic disease is confined to the liver. Accurate measurement of PHR using the technique described is recommended for the evaluation of this group of patients.

## Acknowledgements

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# Multiple-fibre low-power interstitial laser hyperthermia: studies in the normal liver

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*Multiple four-fibre low-power interstitial laser hyperthermia was performed in the canine liver to establish the parameters with which large areas of thermal necrosis could be made. Using 1·5 W for 670 s (4020 J in total) and a fibre spacing of 1·5 cm, lesions with dimensions of 3·6 × 3·1 × 2·8 cm were achieved in 75 per cent of those attempted. There was no mortality and a low morbidity rate. These lesions could be visualized in both their development and resolution using ultrasonography. Healing occurred by 1 year. Temperatures in the centre of the heated region were 60°C, which is more than enough to cause thermal cell death. There was good correlation between the temperatures recorded, the sonographic changes seen, and the pathological evidence of necrosis. Multiple-fibre low-power interstitial laser hyperthermia performed with ultrasonic guidance may be of use in the treatment of liver tumours.*

Cancer of the liver, whether primary or secondary, has a poor prognosis. A small percentage is suitable for treatment by surgery, with a varying (25–60 per cent) 5-year survival rate[1]. In the UK, there are about 17000 deaths each year from colorectal cancer, about half of which are associated with liver metastases[2]. Survival after the development of liver metastases depends on the amount of the organ involved, expressed as percentage hepatic replacement[3,4].

Hyperthermia, or the use of heat for medical purposes, has been recorded since antiquity[5]. Coley-Nauts *et al.* demonstrated the regression and cure of tumours (mostly sarcomas) by injecting a mixture of toxins of *Streptococcus pyogenes* and *Bacillus prodigiosus* into the tumour[6], with the development of a temperature of 41°C for several hours. Since then, it has been well established that cells are sensitive to heat; a temperature between 42 and 45°C for 1 h is associated with cell death[7], probably due to protein denaturation[8,9]. The effect on tumours is mixed and complex, heat probably causing a vascular steal around the tumour and, within, vasoconstriction, reduced pH, hypoglycaemia, increased capillary permeability and oedema[10]. That tumours start nearer these conditions for reduced growth and cell death may explain the observations that tumours (rather than individual cells) are more heat-sensitive than normal tissues[10]. This small differential is lost over 50°C.

Pathological studies of those dying from liver failure after hyperthermic treatments for drug-resistant gonococcal urethritis[11] and after heatstroke showed generalized inflammatory changes and centrilobular necrosis[12,13]. The use of extracorporeal heating to heat the whole liver produced a 25 per cent mortality rate both experimentally and clinically[14,15]. Heating of the liver by localized or regional hyperthermia (that is, to the liver and upper abdomen) by radiofrequency heating caused patchy liver damage, but was not fatal and healing occurred[16,17]. The experimental use of heat to produce focal damage in both normal liver and inoculated liver tumours was associated with only a low mortality rate[18,19]. Heating the entire liver has high morbidity and mortality rates, whereas heating focal areas has not. Hyperthermia would be a feasible way to induce tumour necrosis if existing methods were better at achieving the required temperatures in the tumour area with minimal damage to surrounding tissues[20].

The neodymium yttrium aluminium garnet (NdYAG) laser has been applied at high powers (50–80 W) to the surface of the liver to cause thermal necrosis[21,22]. This has the disadvantage that light is reflected off the surface; to reach deeper into the liver requires exposure of the surface to unnecessarily high power levels, and it is difficult to control the depth of penetration and effect.

Interstitial therapy is the placement of the delivery point of treatment into the area to be treated. This is invasive but allows treatment to be applied more precisely to the required region with less effect on surrounding tissues. The interstitial placement of a quartz laser light delivery fibre into rat liver and the use of low powers (1–2 W) produced lesions of thermal necrosis up to 17 mm in diameter. These healed by regeneration and fibrosis by 60 days with a minimal mortality rate[23]. The same simple method produced some eradication in the rat of both a dimethylhydrazine-induced colon cancer[24] and a transplantable fibrosarcoma[25], with similar dimensions of thermal necrosis as produced in the liver.

The dimension of the thermal necrosis was, however, too small for general application in the treatment of human tumours. We have therefore developed a multiple-fibre delivery system to try to produce areas of thermal necrosis in the liver of a larger size that might be useful in the treatment of liver tumours. Multiple-fibre applications were made in the canine liver to determine whether it is possible to create large areas of thermal necrosis with safe resolution, to determine the best laser parameters with which to do so, and to study the response of the liver to the development of large areas of thermal necrosis.

## Materials and methods

### *Laser and fibreoptic delivery systems*

The laser used was a CVI Corporation (Albuquerque, New Mexico, USA) NdYAG laser. A small number of experiments were performed with the sequential use of a single 400-μm quartz fibre. This was time-consuming, and subsequently a fibre coupler (an optical component where there is interconnection of a number of optical waveguides by mixing or splitting of all signals in the component) was used to allow the simultaneous use of four fibres. The coupler used was a 1 × 4 (one input fibre, four output fibres) coupler (Canstar Ltd., Scarborough, Ontario, Canada). The fibres were 200 μm in diameter with an outer plastic coating of 40 μm thickness, and were joined by the fused biconic technique. To be of use, a coupler has to split the input light beam as equally as possible, so that there is an equal output from each fibre. This is essential to ensure an equal biological response around each fibre tip. The advantage of a fibre coupler is its small size and that it does not need adjustment at each experiment as the splitting

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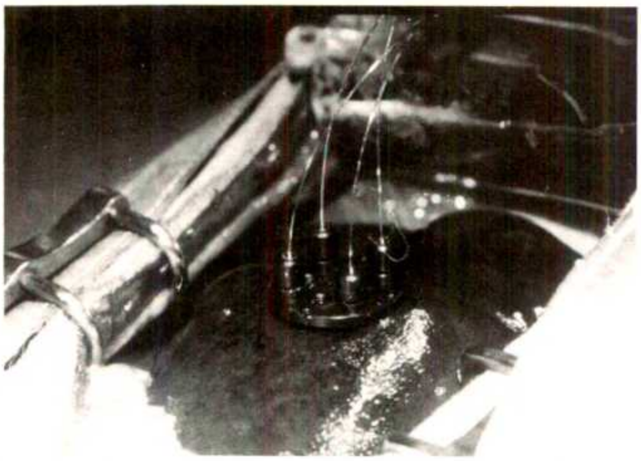

**Figure 1** *Operative picture of four fibres, held in disc and screw collets, placed in the liver. Note the angle of the fibres to maintain slight pressure but allow movement with respiration*

ratio is set on manufacture. The Canstar coupler used did not over-heat and had suitable stability over a range of laser operating currents and outputs[26], with a variation between fibres of 5 per cent.

*Operative details*

Experiments were performed in the canine liver. Premedication consisted of intramuscular fentanyl citrate and fluanisone (Hypnorm, Janssen, Oxford, UK) 0·5 ml/kg and atropine 600 mg. Anaesthesia was induced with methohexitone followed by tracheal intubation; maintenance of anaesthesia was with 0·5 per cent halothane added as required to oxygen. Normal saline 250 ml was given intravenously over the course of the procedure. Benzyl penicillin 300 mg and gentamicin 40 mg were given intravenously at the start of operation, and pethidine 50 mg and metoclopramide 2–5 mg intramuscularly at the end.

An upper midline incision was made and the medial and lateral left lobes of liver freed from peritoneal attachments and delivered into the wound. These were suitable for the creation of potentially large areas of thermal necrosis, while avoiding edge effects; that is, the lesion size being limited by the model size.

When using sequential single fibres, the fibres were placed one after another, with the power output checked between each application. Only seven experiments were carried out with the sequential technique, and only two of these gave overlapping lesions (at a power of 1·5 W and fibre separations of 1 and 1·5 cm). As this technique was so time-consuming and had no advantage over the multiple-fibre technique, all subsequent experiments used the four-fibre system. The multiple fibres for simultaneous application were held in a purpose-designed arrangement of screw collets set in a plastic disc. There were a number of discs with different spacings to allow the gap between fibres to vary from 0·5 to 2 cm. The fibres were thus arranged in the shape of the four corners of a square.

The screw collar on the collet was undone and the fibre was placed through the split pin within; the projecting length was then set with dividers. The screw collet collar was tightened gently to hold the fibre firmly and prevent movement in the line of the fibre. The disc and screw collets allowed the depth of fibre penetration into the liver to be preset and to remain constant throughout the procedure. The horizontal separation of the fibres could also be varied to determine the optimum spacing. Once set up, the plastic disc and fibres could be 'plugged' into the liver (*Figure 1*). The fibres were inserted for 1–1·5 cm. Being 200 μm in diameter, the fibres easily penetrated into the liver with no need for introductory puncture holes.

Thirty-five multiple-fibre experiments were carried out in 18 female ex-breeder beagles. Powers of 0·5, 1 and 1·5 W were used. The time of irradiation varied from 500 to 1500 s, giving a range of total energies used of 1000–6000 J. Fibre spacing was 1, 1·5 and 2 cm. The aim of the work was to develop a system with laser parameters that could be applied clinically. As it became apparent on analysis of results that 1·5 W for 670 s (4020 J) and a fibre spacing of 1·5 cm were the most appropriate settings, more was done with these to assess reproducibility and to allow long-term follow-up of the lesions created.

*Intraoperative monitoring*

The temperature in the centre of the area to be heated was measured with a manganin/constantan multiple-junction thermocouple[27] connected to a purpose-built thermometry system which displayed the temperature on the monitor of a microcomputer throughout the experiment. The thermocouple was positioned by piercing the liver capsule with a needle and then passing the thermocouple into the liver through a central siting hole in the fibre-holding disc. The aim was to place the thermocouple parallel to the four fibres. The thermocouple was inserted out the same distance as the fibres so that the end (the first junction) was in the same horizontal plane as the tips of the laser fibres, each 10·5 mm distant at the corners of the square. It was difficult to position the multiple-junction thermocouple accurately and this, combined with persistent problems with the thermometry system, resulted in only three good recordings of temperatures in the centre (10·5 mm from the fibre tips) and four recordings of the liver surface temperature (18·5 mm from the buried fibre tips) being made.

Intraoperative ultrasonography was performed during four experiments to monitor the development of thermal lesions. Full details of ultrasonic changes in association with interstitial laser hyperthermia are given elsewhere[28]. Intraoperative ultrasonography was used to see whether the thermal damage caused could be visualized and for comparison of ultrasonic with pathological measurements. Ultrasonographic equipment made by Bruel and Kjaer (Naerum, Denmark), Aloka (Tokyo, Japan) and Hitachi (Tokyo) was used with intraoperative probes with operating frequencies of 5–7·5 MHz. Machine availability limited the number of observations.

*Postoperative monitoring*

Blood was taken for liver function tests. Repeat ultrasonographic examinations were carried out on three animals to provide longer follow-up at 1, 3, 5 and (in one) 12 months. This was both transcutaneous and intraoperative, the latter to provide clearer visualization of the liver changes without the problem of the very narrow costal angle, which limited full transcutaneous views. At a second laparotomy, biopsies were taken under ultrasonic guidance.

After the dogs were killed, the liver was removed *en bloc* and the relevant lobe fixed in 10 per cent formalin. After 48–72 h, the lobe was sliced perpendicular to the line of fibre insertion to allow measurement of overlap of areas of thermal necrosis. Sections were 3–6 mm thick. The sum of the thickness of the sections gave the depth of thermal necrosis. If thermal necrosis[23] was visible to the naked eye, measurement to the rim was as accurate macroscopically as microscopically. Sectioning was as described since the depth of thermal necrosis in the line of the fibre would not be expected to vary greatly from that seen with a single-fibre lesion, whereas the area between the four fibres in a horizontal plane would. The overall dimensions of thermal necrosis were measured with fine dividers. The presence of charring at the fibre tip site or in the line of the fibre was noted. For comparative purposes, the largest dimensions are given. After sectioning, relevant subsections were cut and stained with haematoxylin and eosin and with van Gieson stains for histology.

Where an overlapping lesion was suspected, post-mortem angiography of the arterial tree of the treated lobe was performed with dilute barium sulphate.

## Results

*Development of overlapping lesions of thermal necrosis*

Thirty-five experiments were performed to create overlapping lesions of thermal necrosis. None developed in three experiments at 0·5 W. On one occasion there was considerable power loss due to laser malfunction involving three experiments; these and the three at 0·5 W are excluded, leaving 29 experiments for further analysis.

Twenty-two were simultaneous with the multiple-fibre system and seven sequential with single fibres. Of the simultaneous experiments, a fully overlapping lesion developed in 12 but not in ten. In the sequential experiments, overlap developed in two but not in five. *Table 1* gives details of the power used, total energy given, spacing between the fibres, development of an overlapping lesion or not, and method used.

The power found to be most effective as experiments continued for the reproducible production of coalescing lesions was 1·5 W. At this power, a total of 19 lesions were attempted (at 1 and 1·5 cm). Although overlap could be achieved at 1 cm, it could also be achieved at 1·5 cm and, since the object was to find the greatest reasonable fibre separation at which overlap occurred, this was pursued further.

Of 14 overlapping lesions made, the total energy delivered

**Table 1** *Experiments divided into power used and distance between fibres*

| Power (W) | Spacing (cm) | *n* | Overlap Full | Overlap Partial | Overlap None |
|---|---|---|---|---|---|
| 1 | 1 | 3 | – | 1† (6000)<br>1* (2000) | 1† (2000) |
| 1 | 1·5 | 5 | 1* (4000) | 1* (3000)<br>1* (4000) | 1* (6000)<br>1† (4000) |
| 1·5 | 1 | 3 | 1† (6000) | 1† (3000)<br>1† (4000) | |
| 1·5 | 1·5 | 16 | 9* (4000)<br>2* (3000)<br>1† (4000) | 1* (3000) | 1* (3000)<br>2* (4000) |
| 1·5 | 2 | 2 | – | 1* (4000) | 1* (6000) |
| Total | | 29 | 14 | 15 | |

Values in parentheses are joules delivered. Method of causing the lesion: *simultaneous delivery with multiple-fibre system; †sequential delivery with single fibres

**Table 2** *Mean(s.d.) lesion diameters of overlapping thermal necrosis*

| Time of measurement | *n* | Width (cm) | Breadth (cm) | Depth (cm) |
|---|---|---|---|---|
| Immediate | 2 | 3·5 | 2·7 | 2·1 |
| 7 days | 5 | 3·6(0·4) | 3·1(0·5) | 2·8(0·5) |
| 14 days | 1 | 3·7 | 3·0 | 2·2 |
| 30 days | 3 | 2·8(0·2) | 2·3(0·5) | 1·9(0·4) |
| 5 months | 2 | 2·05 | 1·25 | 1·75 |
| 12 months | 1 | 4 charred areas in normal liver with a separation of 1·5 cm | | |

was 4000 J or more in 12 and less (3000 J) in two. In the experiments in which overlap did not occur, the total energy delivered was 4000 J or more in nine and less than this in six.

The majority of exposures were at 670 s, giving 1005 J for each fibre, a total of 4020 J. Of the 16 lesions attempted using 1·5 W with 1·5 cm fibre separation, 12 (75 per cent) were successful and overlapped and four did not. In two of those in which overlap occurred the total energy input was below 4000 J. Of those that failed to overlap, in two there was no power loss, but in the other two there was power loss so that only about 3000 J were delivered. One lesion showed near overlap. The cause of the power loss was the use of an optical beam splitter in which two fibres moved out of alignment in one, and loss of alignment of the input fibre of the coupler due to a faulty connection to the laser head in the other.

When no overlapping or coalescing lesion developed, there was a tendency towards this in eight experiments (that is, where two or three regions around the fibre tips overlapped but not all four). Five of these were with the coupler (simultaneous) and three were sequential. In the remaining seven, four separate lesions only were seen.

### *Change in lesion size with time*

The size of lesions at different times is given in *Table 2* and expressed graphically in *Figure 2*. The formula used for volume calculation was:

$$\text{Volume} = \frac{4\pi \times abc}{3}$$

where $a$, $b$ and $c$ are the semi-axes.

*Figures 3–6* show examples of sections through liver at 0, 7 and 30 days, and at 5 months. From all the overlapping and indeed all the lesions, only one abscess developed at 1 month. This was the only morbidity associated with the procedure; there were no deaths. At the second laparotomies, the surface of the two left lateral lobe lesions was covered with a white fibrinous membrane and there were slight indentations at what was presumed to be the site of fibre insertions. In one, the left medial lobe was densely adherent to the diaphragm. At post mortem, no free fluid or pus was found. Omentum was usually adherent to the involved lobe up to 30 days after operation.

### *Ultrasonography*

*Figure 7* is an ultrasonographic image at the end of the creation of a lesion of thermal necrosis. The white hyperechoic stars are

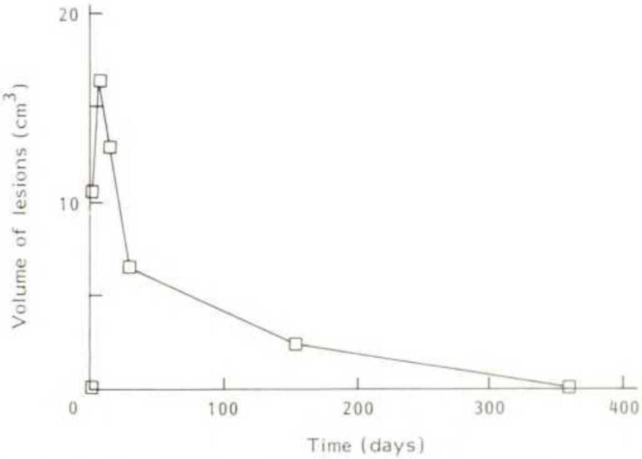

**Figure 2** *Change in size of lesions of thermal necrosis with time*

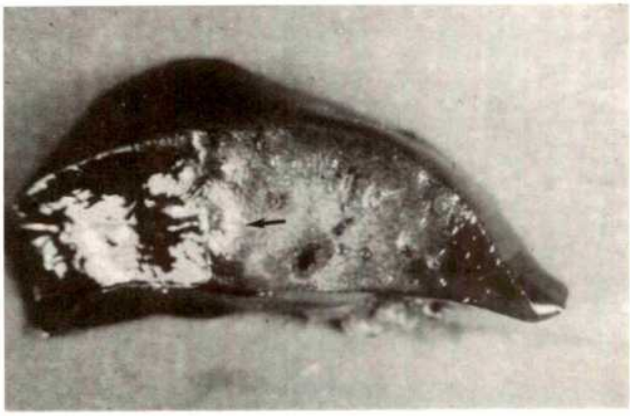

**Figure 3** *Appearance of a lesion of thermal necrosis at 0 days. The black points are charring. There is a clear margin between normal liver and the paler heated liver (arrow)*

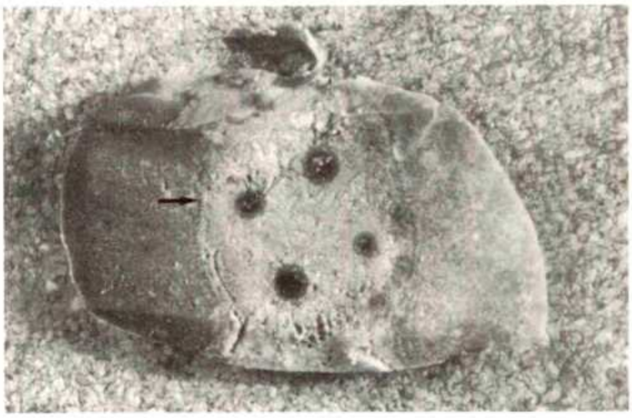

**Figure 4** *A lesion of thermal necrosis at 7 days. The four black spots are charring at the fibre sites. There is a clearly defined margin between the dead and surrounding normal liver (arrow)*

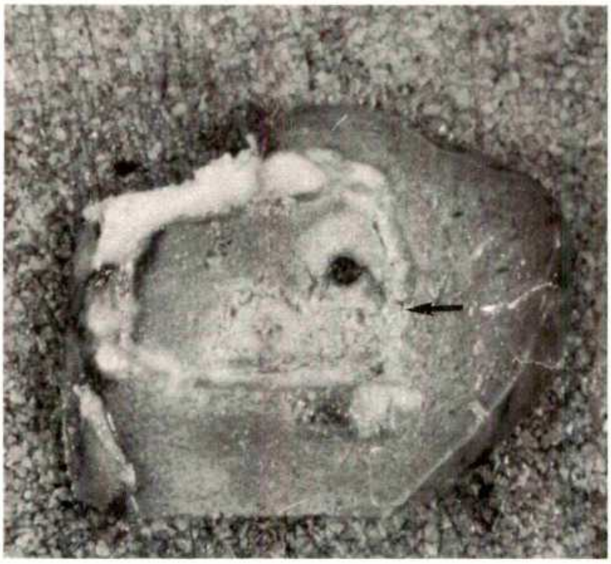

**Figure 5** *A lesion at 30 days. The distinction between necrotic and normal liver is still clear (arrow)*

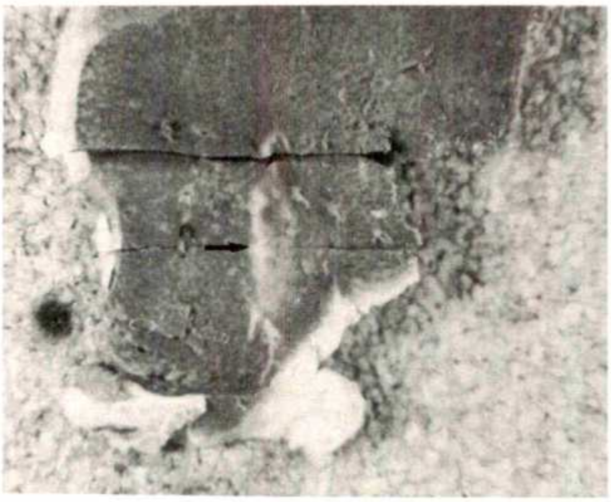

**Figure 6** *A lesion at 5 months with clear distinction between normal and necrotic liver (arrow)*

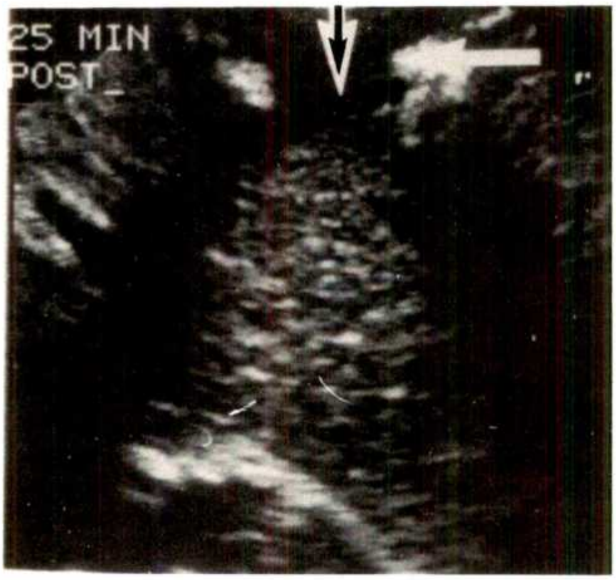

**Figure 7** *Ultrasonographic image of* Figure 3 *with two hyperechoic stars or charring at fibre tips and a hypoechoic area between them (black arrow) and around them (white arrow)*

the small areas around the fibre tips, and the blacker hypoechoic region is the overlapping area that has been heated. Three lesions of thermal necrosis were serially scanned. At 1 month a clearly defined lesion was seen with four echogenic foci at the sites of the fibre tips and a clear margin between affected hypoechoic and normal echoic liver (*Figure 8*). At 3 months the differences from the appearance at 1 month were that the margin between the lesion and surrounding liver was less sharp and the echogenicity of the central area was less hypoechoic and more like normal liver. At 5 months the edge definition was similar to that at 3 months. The echogenicity of the intermediate or affected zone was nearer to that of surrounding normal liver. By 1 year only the four echogenic foci remained, sitting in liver of normal echogenicity.

*Table 3* gives the dimensions of the area that had undergone ultrasonic change. Also in this table are the measurements, where available, of the specimens on which ultrasonography was performed. This allows comparison between ultrasonographic measurements and actual lesion diameters.

### *Histology*

Study of the immediate lesion showed a small cavity around the fibre tip (2 mm), with a zone of charring around this, and outside this an area of vacuolation. The overall diameter of this region measured 3–5 mm. The fibre tips had slight charring on the sides for 3–5 mm from the end, but rarely any on the cut face. Between the fibre tip sites there were normal viable liver cells with early inflammation, but maintenance of the hepatic architecture. Gas spaces were apparent in the liver substance and particularly in the spaces around the portal veins. Indeed, on van Gieson staining, it was apparent that the collagen of the portal venous tributaries had been deranged.

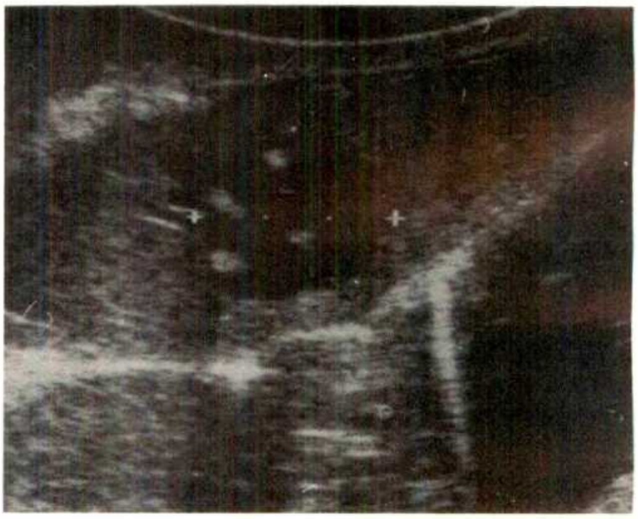

**Figure 8** *Ultrasonographic image of a lesion at 30 days. The four areas of charring are clear, set in a hypoechoic surround, which has a clear margin with surrounding normal liver (+ to +)*

**Table 3** *Ultrasonic measurement of lesions of thermal necrosis compared with actual lesion measurements*

| | Lesion diameter (cm) | |
|---|---|---|
| | Ultrasonic measurement | Measured specimen |
| Immediate | 3·3 × 2·5 | 3·5 × 2·8 |
| 1 month | 3·2 × 3·0 | 2·8 × 2·7 |
| 3 months | 3·0 × 2·6 | |
| 5 months | 2·9 × 2·2 | 2·1 × 1·3 |

These measurements can be compared with those in *Table 2* to allow comparison with the mean total lesion dimensions

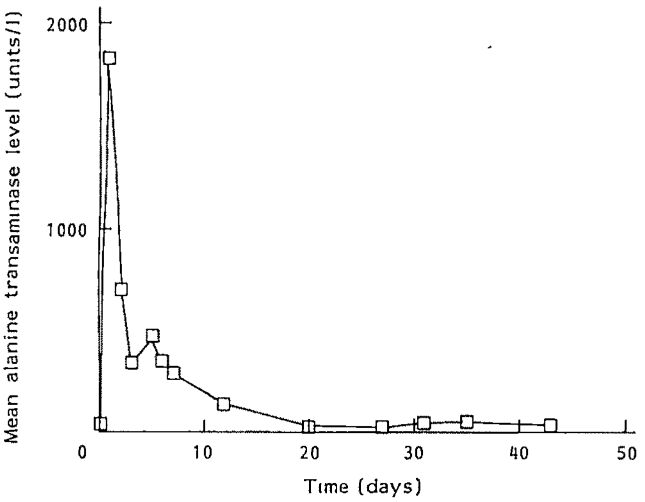

**Figure 9** *Serum alanine transaminase concentration after the formation of a lesion of thermal necrosis*

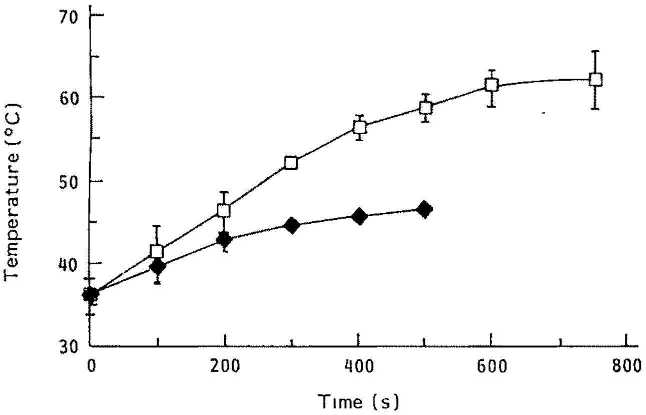

**Figure 10** *Mean(s d ) temperatures recorded in the centre (□) and on the surface (◆) of the liver lobe during creation of lesions of thermal necrosis (all with 1 5 W and a fibre spacing of 1·5 cm for 670 s) The surface recordings ran to only 500 s*

There was no evidence of microvascular thrombosis. At 1 week there was evidence of a fibrous capsule at the edge of the lesion and by now the cells between the points of energy insertion were dead. The dead liver still maintained its architecture. At 1 month there was further fibrosis with, at the edge of the lesion, a bull's-eye-like appearance with fibrosis, then the ingrowth of new blood vessels and biliary canaliculae, then an area of dead liver cells, then an area of lymphocytic infiltration, and then the mass of necrotic tissue. This picture was seen at 5 months, with more fibrosis and regeneration. At 12 months there were four chars set in normal liver.

*Biochemistry*

The picture was one of acute liver damage with a rise in serum alkaline phosphatase and alanine transaminase levels (*Figure 9*). The changes were most marked in the latter, with a dramatic rise followed by a return to normal by 60 days. The pattern for alkaline phosphatase was similar but less marked, but the values remained slightly elevated throughout. The serum bilirubin level was never elevated.

*Temperature measurement*

Thermocouple recordings were made successfully from the centre of the region heated on three occasions. Temperatures were recorded of the surface of the liver, using the same laser parameters on four occasions (1·5 W per fibre for 670 s with a fibre separation of 1·5 cm). *Figure 10* shows the pattern of temperature rise seen in the centre of all three and on the surface. Recording was at one observation per thermocouple junction every 2 s. The temperatures reached in the centre of the overlapping area were about 60°C, more than adequate to cause hyperthermic necrosis.

*Angiography*

At 14–30 days a clear 'hole', with no arterial supply to the area of thermal necrosis, could be seen on angiography, with vessels running around the affected area with a normal pattern to the rest of the lobe.

*Prediction of the development of overlapping lesions*

The possible prediction of the development of an overlapping lesion could be made by palpation of a firm intrahepatic mass, by intraoperative ultrasonography, or by the temperatures recorded, either in the centre of the liver or on the surface. When an overlapping lesion developed, palpation predicted this correctly in ten cases and incorrectly twice. Palpation was correct on all eight occasions that overlap did not occur Temperature measurements predicted the development of an overlapping lesion correctly in seven cases and incorrectly once. Failure to record the temperatures associated with the development of a coalescing lesion correctly predicted no lesion on all six occasions. It was better to measure temperatures within the liver rather than on the surface. Ultrasonography gave a dynamic view of the development of the whole lesion rather than monitoring change at one point as the thermocouples did and, on the five occasions used correctly, indicated that an overlapping lesion had developed. A negative prediction was more likely to be correct than a positive one. Of positive predictions, both palpation and temperature measurement gave false predictions, whereas ultrasonography did not.

## Discussion

The work described here shows that with the correct laser parameters it is possible to produce areas of thermal necrosis that are of dimensions similar to those of detectable human liver tumours With these parameters there was a 75 per cent chance of causing an overlapping lesion of thermal necrosis. The morbidity rate was low, with no mortality. Ultrasonic monitoring of the initial process and of the resolution of the thermal necrosis is important, as this is a practical way of imaging placement of laser fibres, determining the extent of necrosis caused, and following it The correlation between ultrasonography, temperature measurement and pathology means that, at the temperatures used here, the ensuing immediate tissue damage leads to a definite ultrasonographic image and so thermocouple monitoring with all its problems[27] may not be necessary; ultrasonography gives a similar or better indication of the tissue changes occurring.

The healing of the lesion of thermal necrosis is similar to that of a hepatic abscess treated with antibiotics[29]. Here the ultrasonic appearance of the lesion changed more than the size did, with resolution towards normal. It may be that a liver tumour treated in this way, once necrotic, would be dealt with similarly. The initial increase in lesion size with oedema and inflammation, followed by a return to normal with resolution, is similar to that seen with the creation of smaller lesions in the rat liver[23]. The time for resolution was longer as the lesions were larger.

The mechanism by which the necrosis was caused is likely to involve several factors. The temperatures recorded are high enough to have caused cell death on their own[7,10] and if this occurred in tumour it would result in cell death around the fibre tip, making the chance of spread from this point unlikely. The reduction (or cessation) of blood supply, demonstrated by hepatic angiography, and the portal venous damage also contribute, as does the passage of microbubbles (at 100°C) through the tissue

The bull's-eye shape of the zone of inflammatory response at the edge of the necrotic zone is seen with other hyperthermic methods of producing focal liver damage, although in a less marked fashion[16–19,23,30]. It is probably this comparatively avascular ring that gives the hypoechoic edge to the necrotic zone on ultrasonography.

Multiple-fibre interstitial laser hyperthermia allows the production of large discrete areas of thermal necrosis, confirming results of other reports that although heating the whole liver is problematic and of little benefit, focal damage does not have these problems[16–19] The aim of this work was not to produce temperatures in the conventional hyperthermic range of 41–45°C, the use of which causes some inflammatory response and patchy necrosis. This is not enough if the treatment of liver tumours is to be considered, with the problems of limited access, the desirability of a small number of treatments, short treatment times and the necessity of therapeutic success.

There are reports of interstitial hyperthermia systems that could be used in the liver[31], but the temperatures recorded are mostly in gel phantoms and there is no evidence of focal tissue death. Ultrasound[32] can be used to produce hyperthermic damage and has the advantage of being an external application. There are, however, the problems of surrounding tissue damage and, in the liver, of focusing onto the desired point and avoiding ribs and bowel.

Inductive coil radiofrequency hyperthermia has been used to treat patients with liver metastases (in conjunction with radiotherapy and chemotherapy) with subjective improvement but little convincing objective improvement[33], as has a microwave annular phased array[34]. In all of these, external hyperthermia was combined with chemotherapy and/or radiotherapy, and at the very least such treatment has a very low morbidity rate.

Lasers have been used at a variety of powers to cause thermal necrosis in the liver. The early use was at high powers applied to the liver surface[21]. This led to areas of necrosis that healed but when applied to implanted tumours caused dissemination as a result of the ferocity of tissue disruption caused with a pulsed laser. The NdYAG laser has been applied via a purpose-built handpiece at 80–100 W[35] The fibre tip was cooled with circulating saline and the laser fired for ten 1-s bursts (1000 J). The resulting lesion measured up to 2 cm and consisted largely of central vaporization The size of the probe (2·5 mm) and its rigidity mean that its application probably has to be at laparotomy. This method has the advantage of speed Lesions so made could be followed during resolution with ultrasonography, but their speed of creation precludes detailed ultrasonographic study[28]

Modified fibre tips have been used to deliver laser energy interstitially. Hashimoto *et al.*[36] used a modified quartz tip with 5–15 W to treat hepatomas at laparotomy (after irradiating any liver surface tumour with 40–60 W). This was followed by a reduction in tumour size on computed tomography and in serum α-fetoprotein concentration. Sapphire tips have been used to try to achieve greater light diffusion into liver This has been done[37] with a thermocouple computer-linked feedback to try to maintain the temperature at 44°C, which would seem to offer little over other non-laser forms of hyperthermia. If sapphire probes are used, care must be taken if cooling is used as there are reports of fatal gas emboli resulting[38].

The system described here is simple in its design and application compared with all the above. The fibres need only cleaving before use, and the basic ultrasonographic equipment is of a sort available in most hospitals. (An ordinary diagnostic probe can be wrapped in a sterile sheath for intraoperative use )

With the increasing sophistication of diagnostic imaging methods including intraoperative ultrasonography, it is becoming easier to detect small hepatic tumours. These can be detected when occult but soon become overt[3,39] However, there is little point in early detection unless treatment is to be considered

Surgery offers the only hope of cure for liver tumours, primary or secondary, but only a small percentage of those considered are suitable. There is debate over the treatment of colorectal liver metastases, some feeling this to be inappropriate[40] and others that not enough patients are screened or offered treatment[41] Multiple-fibre interstitial laser hyperthermia is a method by which small liver tumours could be treated if detected either at laparotomy or percutaneously[42].

Other possible treatments include cryotherapy[43] and alcohol injection[44] Both of these are done with ultrasonic guidance. Cryotherapy has to be carried out at laparotomy and cannot be repeated easily. Alcohol injection can be done percutaneously but several treatments may be needed and it is less precise than interstitial laser hyperthermia as it is not possible to control the spread of alcohol once injected.

Multiple-fibre interstitial laser hyperthermia is a safe, reproducible method of causing precise amounts of hepatic thermal necrosis that can be monitored in their creation and resolution with ultrasonography. The dimensions of the necrosis caused are similar to those of the smaller detectable human liver tumours and therefore this technique may have an application in their treatment

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# Repeated hepatic resection for recurrent metastases from colorectal cancer

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*Since 1980 120 patients with hepatic metastases from colorectal cancer underwent surgery at the Istituto Nazionale Tumori of Milan. Of these, 34 developed recurrence in the liver only and 11 underwent repeat surgery. The median interval between the two resections was 10 months and operative morbidity and mortality rates were 40 per cent and 9 per cent respectively. Nine patients with adequate follow-up were evaluated and after a median follow-up of 17 months four were alive and disease-free, two were alive with lung metastases and hepatic relapse and three had died. The overall median survival of these patients was 23 months.*

It has been estimated that approximately 30 per cent of radically resected liver metastases from colorectal carcinoma will recur in the liver as primary or single site relapse[1–4]. There are, however, few reports dealing with surgical therapy of these relapses[5–12].

## Patients and methods

From 1980 to 1990, 120 patients with hepatic metastases from colorectal cancer (after preoperative staging with computed tomography, ultrasonography and angiography) were submitted to surgery at the Istituto Nazionale Tumori of Milan. After a median follow-up time of 18 months, 34 developed relapse only in the liver These patients usually received chemotherapy but in more recent years some patients have been selected for further surgery. Eleven patients underwent reoperative hepatic surgery and the characteristics of these are presented in *Tables 1* and *2*.

The median interval between two hepatic resections was 10 (range 8–59) months In patients 2 and 7 a further metastasis was found in the diaphragm and in the ileum and these were resected radically Patient 3 underwent simultaneous resection of a second liver metastasis and a lung metastasis. Intraoperative sonography was not used in these patients. Surgical resection was performed without using an ultrasonic dissector. In all but two patients (nos 1 and 5) resection was considered adequate. Median follow-up time was 17 (range 3–42) months and survival was calculated by the life-table method.

## Results

Major postoperative complications were present in five patients (one biliary fistula, one stenosis of common hepatic duct, one transient hepatic failure, one intraoperative haemorrhage and one subphrenic abscess) and one died during the surgical procedure. Median blood loss was 900 (range 0–9600) ml and median postoperative stay was 13 (range 7–48) days.

After a median follow-up time of 17 (range 3–42) months four patients are alive and disease-free after 15, 17, 24 and 42 months. Three patients are dead from progression of disease (two relapses in the liver and one in the liver and lung) at 12, 22 and 25 months, one is alive with lung metastases after 16 months, one patient is alive with hepatic relapse and lung metastases after 6 months and one has an insufficient period of follow-up.

In an attempt to find some prognostic factors the median survival was analysed according to different variables (*Tables 3* and *4*). The small number of patients precludes an appropriate analysis and it is impossible to discern whether the relationship between the apparent benefit of second intervention and a long interval between the two resections of the liver is significant.

The median survival of these patients is 23 months with a 3-year actuarial survival rate of 36 per cent.

## Discussion

This series adds to existing knowledge in this field (*Table 5*). Some points deserve further consideration.

In evaluating morbidity and mortality it is acknowledged that second hepatic surgery is technically difficult. The rate of mortality and morbidity is comparable to that previously reported[13].

The median actuarial survival of resected patients was 23 months and 40 per cent of these patients were alive and

**Table 3** *Relationship between clinical and biological variables at time of first liver resection and survival*

| | *n* | Survival (months) | Median (months) |
|---|---|---|---|
| Site of primary | | | |
| Colon | 7 | 16†, 24, 25*, 12*, 22*‡, 15*, 42 | 22 |
| Rectum | 2 | 17, 6† | 11·5 |
| Stage of metastases | | | |
| I (H1s) | 3 | 15, 42, 17 | 17 |
| II (H1m, b-H2s) | 5 | 24, 12*, 22*‡, 16†, 6† | 16 |
| III (H2m, b H3s, m, b) | 1 | 25 | 25 |
| Type of surgery | | | |
| Left hepatectomy | 1 | 12 | 12 |
| Right hepatectomy | 3 | 25*, 16†, 6† | 16 |
| Non-anatomical resection | 5 | 24, 22*‡, 15, 42, 17 | 22 |
| CEA level | | | |
| $\leq 50$ mg ml$^{-1}$ | 6 | 24, 12*, 22*‡, 42, 17, 6† | 17·5 |
| $> 50$ mg ml$^{-1}$ | 3 | 28*‡, 15, 16† | 16 |
| Blood transfusion | | | |
| $\leq 500$ ml | 2 | 22*‡, 17 | 19·5 |
| $> 500$ ml | 7 | 24, 25*, 12*, 15, 16†, 42, 6† | 15 |
| Adjuvant therapy | | | |
| Yes | 6 | 24, 25*, 22*‡, 15, 42, 17 | 23 |
| No | 3 | 12*, 16†, 6† | 12 |

CEA, carcinoembryonic antigen; *patient dead; †alive with disease; ‡non-radical surgery

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**Table 1** *Characteristics of patients and first liver surgery*

| Patient no. | Sex | Age (years) | Site of primary (Dukes' classification) | Interval between primary and metastases (months) | Site of metastases (segment) | Stage* | CEA (mg ml$^{-1}$) | Surgery | Blood loss (ml) | Complications | Adjuvant therapy |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | F | 47 | Rectum (B) | 47 | I, II, VI, VII, VIII | H3b | 10 | ERH + NAR | 1800 | – | – |
| 2 | F | 50 | Sigmoid (C) | 26 | III, VI, VII | H1b | 29·3 | Multiple NAR | 900 | – | 5-FU i.a preop. ×7 |
| 3 | M | 48 | Sigmoid (C) | 24 | VII, VIII | H2m | 90·8 | RH | 3000 | – | FUDR i a. postop. ×6 |
| 4 | F | 74 | Sigmoid (C) | 11 | II, IV | H1m | 5·3 | LH | 600 | Biliary fistula | – |
| 5 | M | 53 | Right colon (C) | 14 | VI, VII | H1b | 16·5 | NAR | 500 | – | 5-FU i.p. ×6 |
| 6 | F | 58 | Rectosigmoid (B) | 23 | V, VII | H1s | 367 | NAR | 1300 | – | FUDR portal ×6 |
| 7 | F | 58 | Left colon (C) | 5 | VI, VII | H1m | 170 | RH | 600 | Abscess | – |
| 8 | M | 54 | Transverse colon (B) | 3 | II | H1s | 18·2 | NAR | 600 | – | FUDR i.a. ×6 |
| 9 | M | 66 | Rectum (B) | 52 | VI, VII | H1s | 3·3 | NAR | – | – | 5-FU i p. ×6 |
| 10 | M | 63 | Rectum (C) | 13 | VII, VIII | H1m | 12·7 | RH | 1800 | Local sepsis | – |
| 11 | M | 67 | Left colon (C) | 14 | V | H1s | 24 | NAR | 300 | – | – |

*Gennari classification, CEA, carcinoembryonic antigen, ERH, extended right hepatectomy; NAR, non-anatomical resection; RH, right hepatectomy; LH, left hepatectomy, 5-FU, 5-fluorouracil, FUDR, floxuridine; i.a., intra-arterially; i.p., intraperitoneally

**Table 2** *Characteristics of patients and second liver surgery*

| Patient no. | Interval between first and second (months) | Site of hepatic relapse | CEA (mg ml$^{-1}$) | Surgery | Blood loss (ml) | Complications | Other therapy | Outcome (months after second liver surgery) |
|---|---|---|---|---|---|---|---|---|
| 1 | 11 | Left lobe | 65 | NAR | 9600 | Lethal haemorrhage | – | Intraoperative death |
| 2 | 59 | Right lobe + diaphragm | 5 | NAR + diaphragm resection | 900 | – | FUDR syst × 12 | Disease-free (24) |
| 3 | 21 | Left lobe + lung | 7 | NAR + lung | 900 | – | – | Died (25) |
| 4 | 8 | First segment | 1·9 | NAR | 300 | Biliary fistula | – | Died (12) |
| 5 | 11 | Right lobe | 13 | NAR | 1200 | – | 5-FU syst. ×6 | Died (22) |
| 6 | 10 | Right lobe + first segment | 180 | NAR | 600 | – | 5-FU + folic acid syst. ×6 | Disease-free (15) |
| 7 | 10 | Left lobe + ileum | 6 | NAR + ileal resection | 600 | – | 5-FU + folic acid syst. ×6 | Alive with lung metastases (16) |
| 8 | 32 | Right lobe | 4 | NAR | 2500 | Stenosis of common hepatic duct | – | Disease-free (42) |
| 9 | 9 | Right lobe | 7·5 | RH | 1400 | Transient hepatic failure | – | Disease-free (17) |
| 10 | 10 | Left lobe | 7·2 | NAR | – | – | – | Alive with hepatic and lung relapse (6) |
| 11 | 30 | Right lobe | 109 | NAR | – | Subphrenic abscess | 5-FU + folic acid syst. ×6 | Disease-free (3) |

CEA, carcinoembryonic antigen, NAR, non-anatomical resection, RH, right hepatectomy, 5-FU, 5-fluorouracil; FUDR, floxuridine, syst., systemic

**Table 4** *Relationship between clinical and biological variables at the time of the second liver resection and survival*

| | *n* | Survival (months) | Median (months) |
|---|---|---|---|
| Interval between operations | | | |
| >1 year | 3 | 24, 42, 25* | 25 |
| <1 year | 6 | 22*‡, 15, 6†, 17, 12*, 16† | 15 |
| Site of hepatic relapse | | | |
| Homolobar | 4 | 24, 22*‡, 15, 17 | 19 |
| Heterolobar | 5 | 25*, 12*, 16†, 42, 6† | 16 |
| Type of surgery | | | |
| Non-anatomical resection | 8 | 24, 24*, 12*, 22*‡, 15, 16†, 42, 6† | 15 |
| Right hepatectomy | 1 | 17 | 17 |
| CEA level | | | |
| ≤50 mg ml$^{-1}$ | 8 | 24, 25*, 12*, 22*‡, 16†, 42, 17, 6† | 20 |
| >50 mg ml$^{-1}$ | 1 | 15 | 15 |
| Blood transfusion | | | |
| ≤500 ml | 2 | 12*, 6† | 9 |
| >500 ml | 7 | 24, 25*, 22*‡, 15, 16†, 42, 17 | 12 |
| Adjuvant therapy | | | |
| Yes | 4 | 24, 22*‡, 15, 16 | 19 |
| No | 5 | 25*, 12*, 42, 17, 6† | 17 |

CEA, carcinoembryonic antigen, *patient dead; †alive with disease, ‡non-radical surgery

**Table 5** *Review of the literature on repeated hepatectomy for recurrent metastasis from colorectal primary*

| Author | Year | *n* | Survival rate (%) | Median time of survival (months) | |
|---|---|---|---|---|---|
| | | | | Survivors | Dead |
| Dagradi *et al*[5] | 1987 | 9 | 44·4 | 14 | 20 |
| Lange *et al.*[6] | 1989 | 9 | 53·6 | 6 | 20 |
| Butler *et al*[7] | 1986 | 2 | 100† | 6–17 | |
| Nordlinger *et al.*[8] | 1987 | 3 | 75 | 22 | |
| Joyeux *et al.*[9] | 1987 | 4 | 100* | 18 | |
| Fortner[10] | 1988 | 1 | 100* | 36 | |
| Griffith *et al*[11] | 1990 | 9 | 88 | 33 | |
| Hohenberger *et al.*[12] | 1990 | 6 | | | 23 |
| Present series | 1992 | 10 | 70‡ | 17 | 22 |

*All with disease; †both disease-free, ‡five patients disease-free

disease-free after a median interval of 20 months. It seems that an interval longer than 1 year between first and second liver resection selects a group of patients with an expected median survival of 25 months *versus* 15 months in patients with a shorter interval. These findings are in keeping with the recent report by Hohenberger *et al.*[12] and require validation on a larger number of patients. The role of adjuvant therapy after resection must be evaluated.

Whether favourable survival results are a consequence of effective therapy (the median survival of patients with liver-limited relapse after hepatectomy and treated with chemotherapy is 10 months in this series) or whether they are due to a favourable selection of patients is not known. A small subgroup of patients exists in which a second surgical resection may achieve an acceptable survival. The small number of such patients (*Table 5*) does not allow identification of patients who will benefit from a second surgical approach The possibility of hepatic re-resection should be considered in planning therapy for recurrent hepatic metastases from colorectal cancer.

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# Flushing technique in the management of retained common bile duct stones with a T tube *in situ*

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*Over a 12-year-period, 6046 cholecystectomies and 918 common bile duct explorations were undertaken with 697 stone-positive choledochotomies (76 per cent). Forty patients (5·7 per cent) had retained common bile duct stones with a T tube* in situ. *Twenty-eight patients underwent flushing of the common bile duct with a continuous infusion of heparinized saline solution with parenteral aminophylline to induce relaxation of the sphincter of Oddi. Complete duct clearance was achieved in 17 patients; infusion was stopped in four patients and no deaths occurred. The use of percutaneous stone extraction (Burhenne's technique), gave an overall successful common bile duct clearance rate of 86 per cent. The flushing technique represents the first step in the non-operative management of retained common bile duct stones in patients with a T tube in place. It is a safe and effective method for use in the early postoperative period with a prolongation of hospital stay of not more than 1 week.*

T tube drainage and exploration of the common bile duct (CBD) occurs in 15–25 per cent of all cholecystectomies[1]. This procedure has a lower morbidity and mortality rate than biliary enteric drainage but the incidence of retained CBD stones reaches 10·6 per cent with intraoperative cholangiography alone and 3·6 per cent with rigid or 2 per cent with flexible choledochoscopy[2]. When this occurs the best way to manage retained CBD stones remains a dilemma. Chemical stone dissolution[3,4], percutaneous stone extraction according to Burhenne[5] or with a choledochofibrescope[6], and more recently choledochoscopic ultrasonography or electrohydraulic lithotripsy[7,8] are available. When a T tube remains *in situ* flushing of the CBD[9–14] may be a valuable method of clearing the common bile duct, especially when the stone is less than 15 mm in diameter and located distally to the T tube. Endoscopic sphincterotomy[15,16] or reoperation[17,18] represent a more aggressive attitude, since their morbidity and mortality rates are not insignificant.

This report describes an experience with 28 consecutive patients with retained CBD stones managed with a continuous heparinized saline solution through the T tube with parenteral aminophylline to clear the common bile duct.

## Patients and methods

This retrospective study retrieved computerized patient files of 40 instances of retained CBD stones between January 1977 and December 1989. During the same period, 6046 cholecystectomies were performed with 918 choledochotomies (15·2 per cent). There were 697 stone-positive choledochotomies (75·9 per cent). Intraoperative cholangiography[19] was used and if a CBD stone discovered, choledochotomy and CBD exploration performed. Clearance of the CBD was checked by rigid choledochoscopy[20,21] and T tube drainage was left in place. A T tube cholangiogram was performed 8–10 days later to ensure CBD clearance.

Twelve of 40 patients with retained CBD stones were excluded for the following reasons: one 93-year-old patient refused attempts to remove his retained stone and a 70-year-old patient had spontaneous stone passage. Nine patients with stones greater than 15 mm in size underwent percutaneous stone extraction 8 weeks after choledochotomy, when the sinus tract was matured[5]. These patients were operated on before 1983. The last patient, a 30-year-old woman with multiple CBD and intrahepatic stones underwent choledochojejunostomy with a Roux-en-Y loop.

Of the patients 28 were suitable for the flushing technique with retained CBD stones less than 15 mm in size and with a T tube *in situ*. Patient details are given in *Table 1* and the size and localization of retained stones in *Table 2*.

A continuous infusion of 1000 ml (5000 units) heparinized saline solution was commenced through the T tube during the first 24 h. If the stone was retained and the procedure well tolerated, 1000 ml heparinized saline solution were given in 12 h, followed by 1000 ml in 6 h and 1000 ml in 3 h. Aminophylline (10 mg kg$^{-1}$ day$^{-1}$) was given parenterally to induce relaxation of the sphincter of Oddi and promote stone passage[22]. Biliary duct clearance was checked by T tube cholangiogram. The CBD flushing was stopped if severe pain developed. If a stone was still present the patient underwent Burhenne's percutaneous stone removal, endoscopic sphincterotomy or reoperation. Burhenne's technique was used first with reoperation for fit patients thereafter. Endoscopic sphincterotomy was used for old and frail patients and if signs of cholangitis or acute pancreatitis were present.

**Table 1** *Characteristics of patients with retained common bile duct stones*

| | |
|---|---|
| Sex ratio (F:M) | 19:9 |
| Mean age (years) | |
| F | 54 (20–83) |
| M | 63 (32–84) |
| Clinical presentation at admission | |
| Biliary colic | 12 |
| Cholecystitis | 7 |
| Jaundice | 4 |
| Cholangitis | 3 |
| Biliary pancreatitis | 2 |

Values in parentheses are ranges

**Table 2** *Localization and size of retained common bile duct stones*

| | |
|---|---|
| Localization | |
| Proximal to T tube | 4 |
| Distal to T tube | 24 |
| Size | |
| < 10 mm | 21 |
| 10–15 mm | 7 |

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## Results

There was an incidence of 5·7 per cent of retained CBD stones. With the flushing technique, complete CBD clearance was achieved in 17 of 28 patients within 7 days (*Table 3*). No correlation between the size and localization of the stone(s) and the duration of treatment was found. No deaths occurred. Some of the patients successfully treated with the flushing technique suffered slight and transient colic in the upper right quadrant which usually represented passage of the stone through the sphincter of Oddi since the T tube control cholangiogram showed a cleared CBD. This pain was not associated with clinical or biological signs of acute pancreatitis or cholangitis. Four patients had severe abdominal discomfort and the washout was stopped Two of them underwent a successful percutaneous stone extraction Two patients were re-explored: a 61-year-old man, after previous endoscopic sphincterotomy failure, underwent successful transduodenal sphincterotomy and a fit 76-year-old patient had a stone removed without incident.

The washout method failed in 11 patients One patient had spontaneous stone passage and one an unsuccessful attempt at endoscopic sphincterotomy when transduodenal sphincterotomy showed an impacted stone at the papilla. One patient underwent CBD re-exploration because at 6 weeks he presented with acute pancreatitis associated with four retained stones. Seven of the last eight patients underwent successful percutaneous stone extraction[5]. The last patient had a successful CBD re-exploration with no postoperative complications. *Figure 1* shows the management and the outcome of the 40 patients.

**Table 3** *Results of the flushing technique*

| | |
|---|---|
| Length of treatment (days) | |
| <3 | 7 |
| 3–7 | 21 |
| Morbidity | 4 |
| Mortality | 0 |
| Complete common bile duct clearance | 17 |
| No common bile duct clearance | 11 |

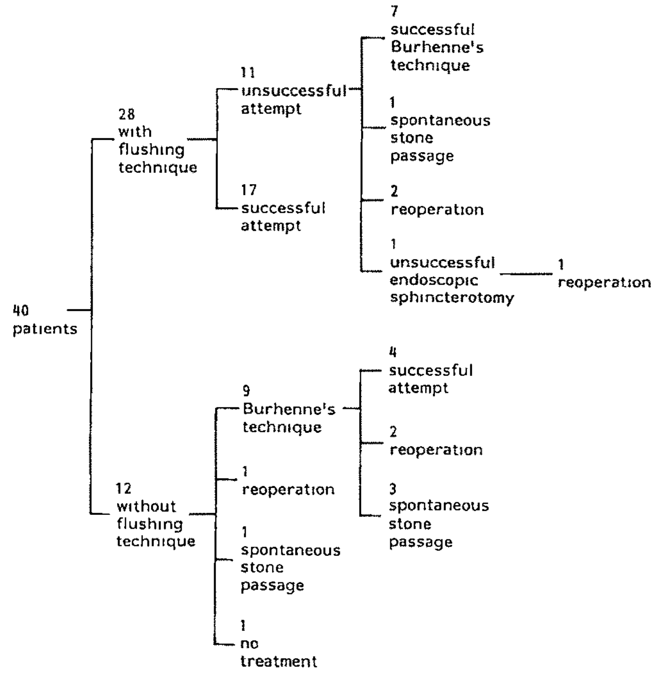
40 patients
28 with flushing technique
11 unsuccessful attempt
17 successful attempt
7 successful Burhenne's technique
1 spontaneous stone passage
2 reoperation
1 unsuccessful endoscopic sphincterotomy
1 reoperation
12 without flushing technique
9 Burhenne's technique
4 successful attempt
2 reoperation
3 spontaneous stone passage
1 reoperation
1 spontaneous stone passage
1 no treatment

**Figure 1** *Management and outcome of 40 patients with retained common bile duct stones and T tube* in situ

## Discussion

Despite the use of intraoperative cholangiography[19] and choledochoscopy[2,20,21] retained CBD stones remain a problem in a teaching institution[23] and occurred in 5·6 per cent of patients. This may be a consequence of reduced biliary enteric drainage since 1977[18].

In recent reviews[1,24], the importance of CBD flushing seems to be underestimated despite a success rate of 50–73 per cent[9,11–14]. As in other studies[9,13], heparinized saline solution was used for CBD flushing and the present results agree with those of Motson[4] that flushing has the most significant effect. Heparin may be useful since some of the retained stones consist of stone debris and clots which are dissolved. Aminophylline is used to induce sphincter relaxation[22,25,26]. Ceruletide, propantheline bromide or glyceryl trinitrate[11,14] may be used. Best results are obtained if the retained stones are located distally to the T tube and are less than 15 mm in size

There is a low morbidity rate[9,11–13] – four patients in this series had severe abdominal pain, but without fever, diarrhoea or vomiting, cholangitis or acute pancreatitis. One patient developed acute pancreatitis 6 weeks after CBD flushing. There were no deaths. These results suggest that flushing should be the first step in non-operative management of retained CBD stones of less than 15 mm located distally to the T tube.

In the review of Neoptolemos *et al.*[3] dissolution agents gave a success rate of 60–80 per cent with mono-octanoin, if the stones were of cholesterol. Treatment had to be interrupted in 9 per cent of patients because of side-effects (15–40 per cent suffered from abdominal pain, nausea, vomiting or diarrhoea). Methyl-*t*-butyl ether may be more effective but the morbidity and mortality rates from its use are not well known.

Percutaneous stone extraction can give a success rate of 95 per cent with a low morbidity rate (4 per cent) and no mortality[5].

Burhenne's technique after the flushing method allowed an overall successful CBD clearance rate of 86 per cent (24 patients) in this study.

More recently T tube tract choledochoscopic ultrasonography and electrohydraulic lithotripsy has achieved a success rate of more than 90 per cent, with minor complications[7,8] These techniques may play a role in the future but require expensive equipment and are currently available in only a few specialized centres.

Endoscopic sphincterotomy or reoperation may have to be considered but their morbidity and mortality rate are not insignificant[15–18].

Heparinized saline washout of the common bile duct is a simple and safe technique for the treatment of retained CBD stones with a T tube *in situ*.

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# Announcement

## Eurosurgery 1992

The 2nd European Congress of Surgery under the auspices of Eurosurgery will take place in Brussels in June 1992. This meeting will pursue the aims of Eurosurgery to promote research and training in surgery.

There will be national sessions sponsored by the Associations of Surgery of all participating nations. Areas of topical interest will be covered in symposia and free paper sessions in areas of general interest and in the specialist fields of abdominal, thoracic, transplantation, trauma, paediatric, endocrine, plastic and vascular surgery. There will be several symposia related to surgical training.

The abstracts of the free paper communications will be published in a special supplement of *The British Journal of Surgery*.

Further details and registration forms may be obtained from the Congress of Secretariat Eurosurgery 1992, Brussels International Trade Fair, Place de Belgique, B1020 Brussels, Belgium. Telephone· 322 477 0457. Facsimile: 322 477 0391.

Br. J. Surg. 1992, Vol. 79, February,
152–155

# Pylorus-preserving *versus* standard pancreaticoduodenectomy: an analysis of 110 pancreatic and periampullary carcinomas

*Pylorus-preserving pancreaticoduodenectomy (PPPD) has received increasing attention as a physiological alternative to the standard pancreaticoduodenectomy (PD) in patients with adenocarcinoma of the pancreatic head or the periampullary region. We evaluated mortality, morbidity and survival in 110 patients with pancreatic carcinoma* ($n = 53$) *or periampullary carcinoma* ($n = 57$)*. In each group 31 patients underwent PD, the remainder PPPD. There were no differences in age, sex and tumour stage (UICC 1987) between patients undergoing PPPD or PD. Median follow-up was 24 months. There were no significant differences in mortality and morbidity rates between procedures. The mode of resection had no influence on survival in patients with periampullary carcinoma. Patients with pancreatic carcinoma who underwent PD had a significantly better survival rate compared with those who underwent PPPD* ($P \leqslant 0{\cdot}05$)*. This was particularly so in patients with stage III tumours* ($P = 0{\cdot}007$)*. These data suggest that in patients with ductal carcinoma of the head of the pancreas, PD provides better survival than PPPD. However, PPPD appears to achieve equivalent results to PD in patients with periampullary carcinoma.*

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Single cases of pancreatic and duodenal resections have been reported since the end of the 19th century[1]. The modern era of surgery of the pancreas, however, did not start until the report of a pancreaticoduodenectomy by Whipple *et al.* in 1935, which was performed as a two-stage procedure[2]. In this original description the pylorus and distal portion of the duodenum were closed and gastrointestinal continuity was re-established by a gastrojejunostomy. The classic one-stage pancreaticoduodenectomy (PD), consisting of a two-thirds gastric resection, pancreaticojejunal anastomosis and choledochojejunostomy, was performed independently by Trimble *et al.*[3] and Whipple[4] in 1941.

Pylorus-preserving pancreaticoduodenectomy (PPPD) leaving the functioning pylorus at the gastric outlet was first reported in 1944 by Watson[5], who resected the head of the pancreas in a patient with a tumour of the papilla of Vater and performed a duodenojejunostomy to re-establish gastrointestinal continuity. This procedure did not receive attention until it was reintroduced in 1978 by Traverso and Longmire[6]. They suggested that preservation of the distal stomach, pylorus and proximal duodenum might improve postoperative gastrointestinal function because it should eliminate the side-effects of gastric resection (dumping and malnutrition). Furthermore, it was thought that leaving the pyloric sphincter intact would decrease the incidence of jejunal ulceration, and they argued that a limited resection is associated with a shorter operating time.

PPPD has been used increasingly in the treatment of patients with benign disorders requiring pancreaticoduodenectomy (such as chronic pancreatitis) in whom a resection of the distal stomach, pylorus and proximal duodenum appears unnecessary Long-term follow-up of these patients tends to show better gastrointestinal function following this procedure than after PD[1]. In recent years PPPD has also been used in patients with periampullary tumours or carcinoma of the head of the pancreas[7]. Whether this limited resection compromises the radicality of tumour removal according to the principles of surgical oncology is, however, unclear. In the present study mortality, morbidity and survival rates after PD and after PPPD were compared in patients with periampullary tumours or carcinoma of the head of the pancreas.

## Patients and methods

Between July 1982 and August 1990, 446 patients with carcinoma of the head of the pancreas or periampullary region were admitted to the Department of Surgery of the Technische Universität München; 217 of these patients (48·7 per cent) did not undergo surgery because of advanced tumour stage or functional insufficiency for surgery On preoperative staging 132 patients were thought to have resectable tumours, which at operation were found to be unresectable in 22, the remaining 110 patients underwent pancreaticoduodenectomy Those patients who on preoperative staging or surgical exploration had unresectable primary tumours or distant metastases ($n = 119$) had a palliative drainage procedure only.

Pancreaticoduodenectomy was performed in 110 patients of whom 53 (48 2 per cent) had a ductal carcinoma of the head of the pancreas and 57 (51·8 per cent) had a carcinoma of the periampullary region (distal portion of the common bile duct, 23 cases, papilla of Vater, 34 cases). The mean (range) age of the patients who underwent resection was 61·5 (27–78) years. There were no significant differences in the age and sex distribution between patients with pancreatic or periampullary tumours (*Table 1*). The single-stage procedure with distal gastric resection (ductal carcinoma of the pancreas, 31 cases; periampullary carcinoma, 31 cases) was performed on 62 patients, the remaining 48 (ductal carcinoma of the pancreas, 22; periampullary carcinoma, 26) underwent PPPD as described by Traverso and Longmire[6]. The decision to perform either PD or PPPD was made according to the preference of the senior surgeon performing the operation. two of five surgeons preferred PPPD All resected specimens were assessed histopathologically Of the patients with

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**Table 1** *Characteristics of patients who underwent standard pancreaticoduodenectomy (PD) or pylorus-preserving pancreaticoduodenectomy (PPPD)**

| | Adenocarcinoma of the head of the pancreas ($n = 53$) | | Periampullary carcinoma ($n = 57$) | |
|---|---|---|---|---|
| | PD ($n = 31$) | PPPD ($n = 22$) | PD ($n = 31$) | PPPD ($n = 26$) |
| Sex ratio (M.F) | 12:19 | 10 12 | 20·11 | 18:8 |
| Mean (range) age (years) | 60 (40–77) | 64 (48–78) | 60 (27–77) | 64 (41–79) |
| Stage$^8$ | | | | |
| I | 14 | 5 | 7 | 5 |
| II | – | 1 | 9 | 3 |
| III | 17 | 16 | 5 | 5 |
| IV | – | – | 10 | 13 |
| Tumour grade$^8$ | | | | |
| Good | 13 | 3 | 11 | 6 |
| Moderate | 11 | 12 | 13 | 11 |
| Poor | 7 | 7 | 7 | 9 |
| Anaplastic | – | – | – | – |
| Residual tumour$^8$ | | | | |
| $R_0$ | 14 | 11 | 25 | 20 |
| $R_1/R_2$ | 17 | 11 | 6 | 6 |

*Differences were not significant (PD *versus* PPPD within each group, Fisher's exact test (two-tailed))

PPPD two had microscopic residual tumour at the resection margin of the duodenum; these patients subsequently underwent a distal gastrectomy. Consequently, these patients were considered to have had a PD for the subsequent analysis.

The TNM classification, grading, the presence of residual tumour, and involvement of perineural spaces were assessed according to the UICC 1987 criteria[8]

All patients were seen at 6-month intervals in the tumour follow-up clinic or were followed by telephone contact with the referring physician. Median (range) follow-up was 24 (8–92) months. Survival rates were calculated according to Kaplan and Meier[9]. Statistical differences between the groups were determined using the Gehan–Mantel test and Fisher's exact test of proportion as indicated A $P$ value $\leqslant 0{\cdot}05$ was considered significant.

## Results

One patient in each group died within 30 days of the procedure resulting in an overall mortality rate of 1·8 per cent. There were no significant differences in morbidity between the two procedures (*Table 2*). A temporary clinically evident delay in gastric emptying was observed in nine patients who underwent PPPD, but this usually resolved within 6 weeks. Ulceration at the gastrojejunal anastomosis occurred in four patients who underwent PD; ulceration at the duodenojejunal junction was seen in two patients with PPPD. All ulcers healed with medical therapy with $H_2$-receptor antagonists.

The distribution of UICC stage, tumour grade and the presence of residual tumour in patients with pancreatic or periampullary tumours are shown in *Table 1*. There were no significant differences in these prognostic factors between the patients who underwent PD or those undergoing PPPD within the subgroups of patients with pancreatic carcinoma and periampullary carcinoma. The numbers of patients with stage I and stage III pancreatic carcinoma who had radical or non-radical resection were similar for PD and PPPD (*Table 3*).

The median survival time and 5-year survival rate were significantly higher for patients with periampullary carcinoma (19 months, 24 per cent) compared with patients with pancreatic carcinoma (12 months, 6 per cent), $P \leqslant 0{\cdot}05$.

In patients with pancreatic carcinoma, the overall survival rate was significantly higher for those who underwent PD than those who had PPPD ($P \leqslant 0{\cdot}05$, *Figure 1*). When analysed according to the UICC stage, the mode of resection had no influence on survival in patients with stage I ($n = 19$) disease. Only one patient had a stage II tumour. A significantly better survival rate in patients with stage III carcinoma of the pancreas was, however, associated with PD ($P = 0{\cdot}007$, *Figure 2*).

In patients with a periampullary carcinoma the operation performed had no significant influence on the survival rate of the entire patient group (*Figure 3*) or survival rates assessed according to the UICC tumour stage.

## Discussion

Surgery remains the mainstay of therapy for pancreatic and periampullary carcinomas and surgical resection of the tumour provides the only chance of cure. Improvement of surgical technique, increased surgical experience and advances in

**Table 2** *Morbidity of standard pancreaticoduodenectomy (PD) and pylorus-preserving pancreaticoduodenectomy (PPPD)*

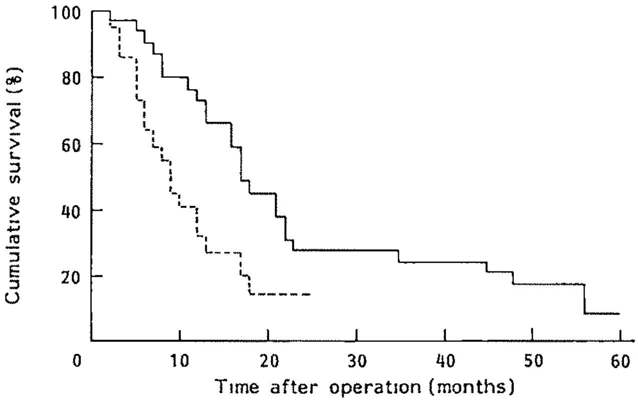
| | PD ($n = 62$) | PPPD ($n = 48$) |
|---|---|---|
| Pancreatic fistula* | 13 (21) | 14 (29) |
| Wound infection | 5 (8) | 4 (8) |
| Bile fistula | 2 (3) | 1 (2) |
| Bleeding (requiring reintervention) | 1 (2) | 1 (2) |
| Delayed gastric emptying (temporary) | 0 | 9 (19) |
| Anastomotic ulceration | 4 (7) | 2 (4) |

Values in parentheses are percentages. *No fistula-related mortality; two reoperations required

**Table 3** *Distribution of $R_0$ and $R_1/R_2$ resections in patients with cancer of the head of the pancreas separated by UICC stage and operation performed*

| | PD | | PPPD | |
|---|---|---|---|---|
| Stage | $R_0$ | $R_1/R_2$ | $R_0$ | $R_1/R_2$ |
| I ($n = 19$) | 9 (64) | 5 (36) | 4 (80) | 1 (20) |
| II ($n = 1$) | 0 | 0 | 1 | 0 |
| III ($n = 33$) | 5 (29) | 12 (71) | 6 (38) | 10 (62) |
| Total | 14 | 17 | 11 | 11 |

Values in parentheses are percentages PD, pancreaticoduodenectomy, PPPD, pylorus-preserving pancreaticoduodenectomy



| No. of patients | | | | | | |
|---|---|---|---|---|---|---|
| PD | 25 | 14 | 9 | 8 | 4 | 1 |
| PPPD | 10 | 3 | – | – | – | – |

**Figure 1** *Cumulative survival curves for patients with ductal carcinoma of the head of the pancreas who underwent standard pancreaticoduodenectomy (PD, n = 31, ——) or pylorus-preserving pancreaticoduodenectomy (PPPD, n = 22, ---) PD was associated with a significantly higher survival rate* (P $\leqslant$ *0·05, Gehan–Mantel test)*

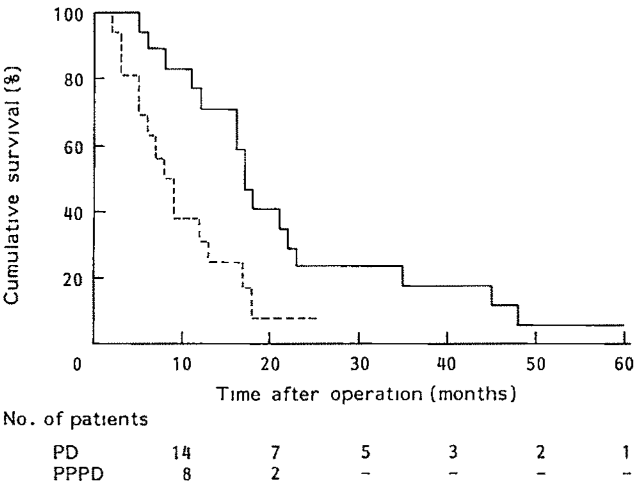


**Figure 2** *Cumulative survival curves for patients with stage III ductal carcinoma of the head of the pancreas who underwent standard pancreaticoduodenectomy* (*PD*, n = *17*, ——) *or pylorus-preserving pancreaticoduodenectomy* (*PPPD*, n = *16*, – – –) *PD was associated with a significantly higher survival rate* (P = *0·007*, *Gehan–Mantel test*)

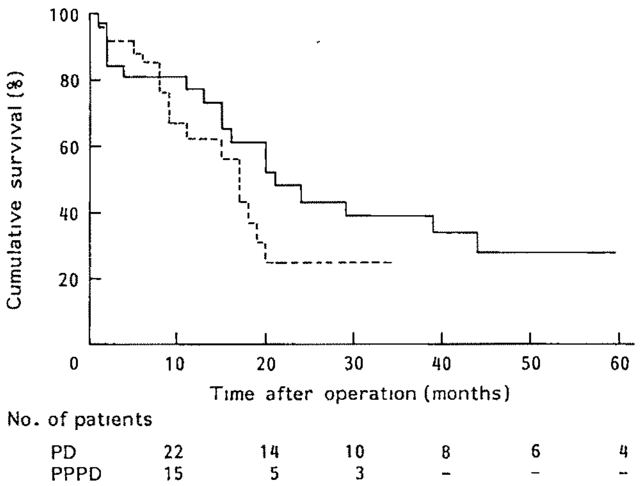


**Figure 3** *Cumulative survival curves for patients with periampullary carcinoma who underwent standard pancreaticoduodenectomy* (*PD*, n = *31*, ——) *or pylorus-preserving pancreaticoduodenectomy* (*PPPD*, n = *26*, – – –) *There were no significant differences between the two procedures* (*Gehan–Mantel test*)

perioperative intensive care and parenteral nutrition have substantially decreased the risk of pancreaticoduodenectomy in recent years. This is reflected in a decrease in the operative mortality rate from over 20 per cent to below 5 per cent in several large centres throughout the world[7,10]. The 30-day mortality rate of 1·8 per cent in this study compares favourably with these figures Pancreaticoduodenectomy therefore has become a safe procedure in experienced hands[11].

The morbidity and functional side-effects of PD are, however, considerable A limited resection, that is, PPPD as performed for benign disease, has therefore been proposed for patients with periampullary carcinomas or carcinoma of the head of the pancreas. Whether PPPD compromises the oncological radicality of the resection in patients with carcinoma is, however, controversial. While Moosa and Davies[11] and McAfee *et al.*[12] maintain that PPPD does not allow adequate resection of pancreatic or periampullary tumours, Grace *et al.* could find no difference in survival rates between PD and PPPD[1]. The value of these studies is limited, since in most reports[1,7,13,14] survival rates for the various procedures were not analysed according to the localization of the carcinoma, or for stage of the disease. In this study the results of PD and PPPD have been compared separately for carcinoma of the head of the pancreas and the periampullary region and for various stages of the disease classified according to the UICC 1987 criteria. In our opinion, this approach alone allows adequate conclusions on the indications for limited resection in patients with carcinoma of the pancreas or the periampullary region.

In the present study there were no significant differences in age, sex, tumour stage, grading or presence of residual tumour after resection between patients who had PPPD or PD within the subgroups of pancreatic and periampullary carcinoma. Compared with PPPD, PD was associated with a significantly higher survival rate in patients with pancreatic carcinoma, and this was most obvious in patients with stage III carcinomas. This suggests that PPPD does not allow oncologically adequate resection of ductal carcinomas of the head of the pancreas, this is supported by the observation of tumour recurrence at the duodenojejunal anastomosis in three patients in the series of Sharp *et al.*[15]. (Two patients in the present series had microscopic residual tumour at the resection margin of the duodenum.) Even if the proximal duodenum or the distal stomach are not infiltrated by the tumour, removal of these organs may allow complete removal of the perigastric and retropyloric lymph nodes[11]. This increased radicality of resection may not be necessary for patients with periampullary carcinoma because there was a similar survival rate for corresponding tumour stages for the two procedures in patients with periampullary carcinoma. In our opinion, this may be due to a difference in lymphatic drainage between pancreatic and periampullary carcinoma.

There were no significant differences in mortality and morbidity rates between procedures. In this respect limited resection does not appear to offer any advantages over PD. Of interest is the observation of a temporary delay in gastric emptying in 19 per cent of patients who had PPPD. This has also been observed by others and is thought to be due to denervation and oedema[1,12,16].

In summary, the data presented here indicate that PPPD does not allow for oncologically adequate resection of advanced tumours of the head of the pancreas. Since the presence of stage III disease in patients with pancreatic carcinoma can be determined only by final histopathological examination this observation has led us to restrict the use of PPPD to tumours of the duodenum, ampulla of Vater or distal common bile duct. The procedure of choice for the resection of carcinoma of the head of the pancreas remains PD with distal gastric resection.

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## Surgical workshop

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# A simple device for open laparoscopy

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Laparoscopic cholecystectomy is rapidly becoming the accepted way to remove the gallbladder. However, this acceptance and the attractions of the technique must not be allowed to disguise the fact that there are inherent risks, which are greater for surgeons who are not experienced in the use of the laparoscope.

Insertion of the Verres needle to establish the pneumoperitoneum and subsequent insertion of the trocar and cannula carry some risk, which is minimized if precautions are taken. There is a greater risk if the patient has had previous surgery, especially if the scar is close to or involves the umbilicus. It is recommended that the Verres needle is inserted with the patient in a head-down position; many surgeons recommend insertion of a urinary catheter and a nasogastric tube. It is possible to insert the Verres needle into the abdomen at a site remote from any scarring, but this does not obviate the danger completely. Verres needles, trocars and cannulae have been modified by a number of instrument companies to incorporate safety guards to protect the viscera from damage. However, there is still a small but significant risk of organ damage using the blind puncture technique.

Open laparoscopy was developed to obviate the need for a blind puncture. A small incision is made, which need be little larger in most patients than that necessary for the insertion of the usual trocar and cannula by the blind technique, and deepened to the linea alba, which is picked up with two pairs of Littlewoods forceps. The incision is then continued through the linea alba and the peritoneum is picked up between haemostats and opened under direct vision. The open laparoscopy cannula is then inserted and tied in. The instrument is equipped with a sliding external obturator which is then forced into the wound to reduce gas leakage, but it does not stop it completely and sometimes a degree of surgical emphysema occurs.

Because of the demand, laparoscopic equipment is at present difficult to obtain. The following simple alternative, which can be constructed in any operating theatre in a matter of minutes, is recommended. Over the end of the usual 11-mm cannula (without the sharp pointed trocar) is forced the distal part of a soft-seal endotracheal tube (*Figure 1*). It is important that the distal end of the cannula projects a few millimetres beyond the end of the endotracheal tube so that the small side holes on the cannula which allow gas flow are not obstructed. This was first achieved with a 9·5-mm endotracheal tube by soaking it in very hot water for a few minutes beforehand. A 10- or 10·5-mm endotracheal tube is easier to use, but is not always readily available. The tube must be shortened, but it is important to dissect out the balloon channel down one side so that this is not damaged. The device, thus assembled, is inserted into the abdomen through a small incision and under direct vision. The balloon is inflated and is held back against the abdominal wall by the assistant who is controlling the camera. The operation can then proceed in the usual way. Subsequent trocars and cannulae can be inserted safely by visualizing their entry from the inside. At the end of the operation the balloon cannula can be removed by deflating the balloon. The open incisions for the ports should be closed with sutures in the linea alba. In this centre these wounds are usually infiltrated with bupivacaine.

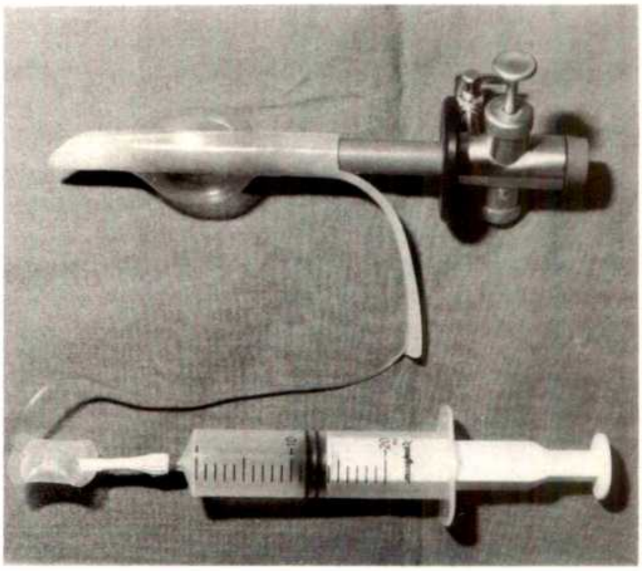

**Figure 1** *The distal part of a soft-seal endotracheal tube is forced over an 11-mm cannula to make a simple alternative to laparoscopic equipment*

The technique of open laparoscopy is to be recommended as it removes much of the worry associated with the blind puncture technique, especially in patients who have had previous surgery. The device described above is now used routinely in our department for such patients.

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# Preoperative assessment of lymph node metastases in patients with gastric cancer: evaluation of the Maruyama computer program

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*The probability of survival of patients with gastric cancer depends upon depth of wall penetration by the primary tumour and metastatic lymph node burden. Radical lymphadenectomy may lead to prolonged survival but with increased morbidity. A computer program from Maruyama, National Cancer Centre, Tokyo enables evaluation of individual survival time and infiltration of lymph nodes. This analysis was applied to a German population. Computer-aided predictions were determined retrospectively using the prognostic factors of sex, age, Borrmann classification, histology, depth of wall penetration, location and diameter of the tumour. Data were collected from 222 patients at the Technical University of Munich (median age 66 years, sex ratio (M:F) 2:1), who had been operated on (72 per cent total gastrectomy, 28 per cent subtotal gastrectomy) for gastric cancer. The predicted results were compared with the postoperative pathological findings. The prediction of node metastases was highly accurate (lymph nodes 13–16, 96 per cent; 7–12, 89 per cent; 1–6, 82 per cent). These computer predictions may provide perioperative information of therapeutic value.*

The role of lymphadenectomy in surgery for gastric cancer is controversial[1–7]. It may be of value in patients who have only a few lymph node (LN) metastases[8,9], but this group of patients is difficult to identify before operation. Maruyama *et al.* analysed data from 3040 patients operated on for gastric cancer in the National Cancer Centre of Tokyo (NCC Tokyo), and from this analysis a computer program was developed for the evaluation of the survival time and the infiltration of lymph nodes in the individual case[6].

This paper evaluates the computer program in a cohort of German patients with gastric cancer to examine the validity of its predictions in this population.

## Materials and methods

### *Computer program*

'Preoperative estimation of survival rate, type of recurrence and lymph node status of patients with gastric cancer'[6].

Data from 3040 patients who had undergone resection for gastric cancer in the Division of Gastric Surgery of NCC Tokyo between 1 January 1969 and 31 December 1983 were analysed retrospectively. Factors influencing survival and the number and location of LN metastases were analysed by multivariate analysis[10]. The most important prognostic factors were sex, age, Borrmann classification[11], depth of wall penetration, site, size and histology of the tumour.

A computer program was established for the individual evaluation of prognosis; this was investigated prospectively in 1000 further patients[12].

### *Patients*

Data for the 3040 Japanese patients were compared with those for 222 German patients with gastric cancer. These patients (rate of resection 86·5 per cent) were operated on between 1 April 1986 and 31 October 1989 in the Department of Surgery of the Technical University of Munich (TU Munich). The data were collected during a German multicentre study[9]. The median age of the population was 66 years with a male:female ratio of 2:1 and a median follow-up of 22 months. The 3040 patients of the NCC in Tokyo had a median age of 57 years and a male:female ratio of 2:1.

### *Operative procedures*

Of the German patients studied 72 per cent underwent total and 28 per cent subtotal gastrectomy. Distal subtotal gastrectomy was performed in 69 per cent of Japanese patients, total gastrectomy in 25 per cent and proximal subtotal gastrectomy in 6 per cent.

Regional LN involvement was documented according to the pathological classification (pN) of the Union Internacional Contra la Cancrum (UICC)[13] and the Japanese Research Society for Gastric Cancer[14] (*Figure 1*). In TU Munich the standard procedure for total and subtotal gastrectomy included *en bloc* lymphadenectomy with resection of the nodes in positions 1–12 and LN13, that is $N_1$ and $N_2$ in the UICC classification[15]; nodes 14, 15 and 16 were removed if macroscopically suspicious. In NCC Tokyo LN positions 1–16 were palpated and if necessary evaluated by frozen section during operation. The perigastric nodes except the nodes on the left side of the cardia (LN2) in distal gastrectomy were removed *en bloc* with the stomach while other positions were resected separately or in groups. When metastases were present the aim of dissection was to provide a margin of uninvolved lymph nodes distally[16]. The depth of invasion into the stomach wall was noted, as were metastases in lymph nodes dissected from the fresh specimen. An average of 30 nodes for Japanese patients and 48 nodes for German patients was noted.

### *Extent of resection*

The R classification of the UICC (1987) was used to determine the residual tumour status after surgery: $R_0$, no residual tumour; $R_1$, microscopically detectable residual tumour; $R_2$, macroscopically visible residual tumour. Of the patients treated in TU Munich 77 per cent underwent $R_0$ resection. A comparable classification has not been used for the Japanese patients: the rate of so-called 'non-curative resections' was almost equivalent to stages $R_1$ and $R_2$ and represented 19·5 per cent of Japanese patients (i.e. 80·5 per cent of the Japanese patients underwent $R_0$ resection).

### *Macroscopic evaluation*

The tumour was classified according to Borrmann[11]. Its size was recorded together with the location to upper, middle and distal thirds of the stomach. Each third was defined by lines dividing both curvatures into three equal parts. The position on the circumference was related to the curvatures and anterior/posterior walls.

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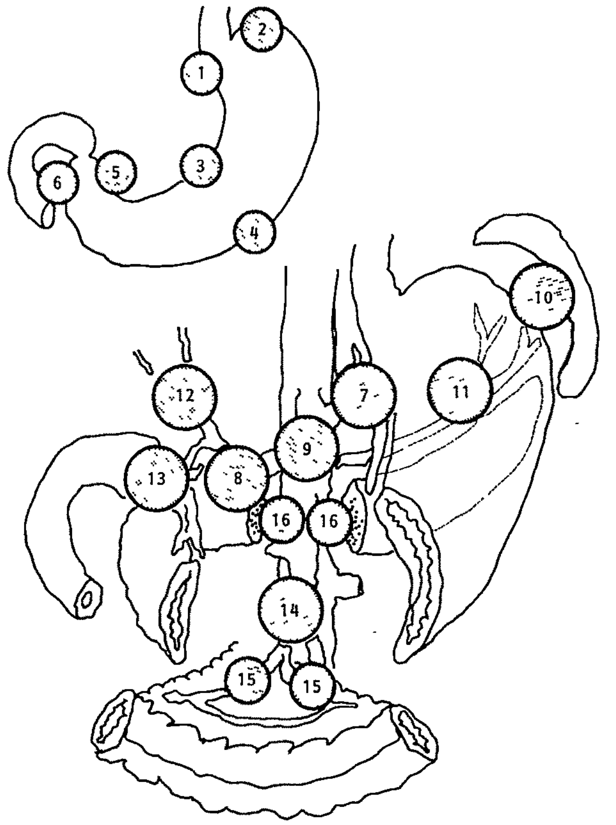

**Figure 1** *Lymph node location in gastric cancer according to the general rules for gastric cancer study in surgery and pathology*[14]. *Perigastric nodes: 1/2, right/left cardiac, 3/4, lesser/greater curvature; 5/6, suprapyloric/subpyloric. Extraperigastric nodes. 7, root left gastric artery; 8, common hepatic artery, 9, coeliac axis; 10, splenic hilus, 11, splenic artery, 12, hepatoduodenal ligament; 13, retropancreatic; 14, mesenteric root, 15, along middle colic vein, 16, along abdominal aorta*

*Histological studies*

Tumours were classified as papillary, tubular well, moderately or poorly differentiated, signet ring cell type, mucinous and rare adenosquamous tumours[15]. Squamous cell carcinomas, carcinoids and non-epithelial tumours were excluded.

*Analysis and statistics*

The prognostic factors of all 222 patients were used and the predictions concerning LN metastases were analysed retrospectively. Descriptive statistical methods (absolute and relative frequencies) were used to describe the distributions of the prognostic factors. The $\chi^2$ test, if necessary with Yates' correction, was used for testing differences with $P < 0{\cdot}01$. The diagnostic accuracy (sensitivity, specificity and predictive values) were calculated for the method. All calculations were performed using the statistical software SPSS/PC+® (SPSS Incorporated, Chicago, Illinois, USA).

## Results

The locations, depth of invasion, tumour stage and macroscopic types are listed in *Table 1*.

*Pathological classification of regional lymph nodes and distant metastases*

*Overall results.* There were significantly fewer patients without LN metastases ($pN_0$ 30·2 per cent) in TU Munich than in NCC Tokyo ($pN_0$ 50·0 per cent) ($P < 0{\cdot}001$); for metastases in lymph nodes 13–16 ($pN_3 = M_1Lym$) (UICC 1987) the situation was reversed ($P < 0{\cdot}001$). The frequencies of $pN_1$ and $pN_2$ stages were not significantly different in either department (*Figure 2*).

The percentage of dissected nodes from different areas was similar in both centres, with some exceptions; the lymph nodes on the left side of the cardia (LN2) were more often resected in TU Munich (96·3 per cent) than in NCC Tokyo (33·8 per cent) ($P < 0{\cdot}001$) (*Table 2*).

The frequency of metastases in node positions 7, 8, 9, 10, 11, 14 and 16 was not significantly different in the two centres. The frequency of metastases in node positions 1, 2, 3, 12, 13 and 15 in TU Munich was double or more that in NCC Tokyo ($P < 0{\cdot}01$); node positions 4, 5 and 6 were more frequent in NCC Tokyo ($P < 0{\cdot}01$) (*Table 2*).

The frequency of distant metastases ($pM_1$) includes the LN metastases in area $N_3$ ($M_1Lym$). At NCC Tokyo 16 per cent of patients had distant metastases at the time of operation compared with 26 per cent at TU Munich.

*Tumour location and metastatic pattern.* The incidence of metastases to perigastric nodes was highest when the tumour was located close to them. Higher frequencies of node

**Table 1** *Frequencies of tumour localization, depth of invasion, stages, and Borrmann classification for patients with gastric cancer in TU Munich and NCC Tokyo**

| | TU Munich ($n = 222$) | NCC Tokyo ($n = 3040$) |
|---|---|---|
| Main area of tumour | | |
| Upper third | 96 (43·2) | 584 (19·2) |
| Middle third | 69 (31·1) | 1298 (42·7) |
| Distal third | 57 (25·7) | 1158 (38·1) |
| Depth of invasion | | |
| $T_1$ | 33 (14·9) | 1097 (36·1) |
| $T_2$ | 86 (38·7) | 539 (17·7) |
| $T_3$ | 71 (32·0) | 939 (30·9) |
| $T_4$ | 32 (14·4) | 465 (15·3) |
| TNM classification | | |
| Stage I | 53 (23·9) | 1319 (43·4) |
| Stage II | 33 (14·9) | 374 (12·3) |
| Stage III | 69 (31·1) | 696 (22·9) |
| Stage IV | 67 (30·2) | 651 (21·4) |
| Borrmann classification† | | |
| Type I | 18 (9·5) | 68 (3·5) |
| Type II | 76 (40·2) | 631 (32·5) |
| Type III | 72 (38·1) | 1046 (53·8) |
| Type IV | 23 (12·2) | 198 (10·2) |

Values in parentheses are percentages. TU, Technical University; NCC, National Cancer Centre. †Classification excludes $T_1$ group; *$P < 0{\cdot}001$ ($\chi^2$ test)

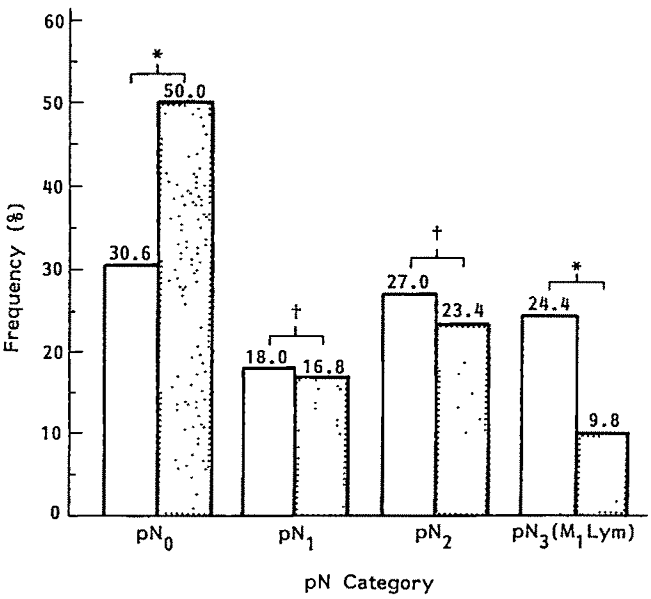

**Figure 2** *Frequencies of lymph node metastases at the Technical University, Munich* (☐) *and the National Cancer Centre, Tokyo* (☐). *$P < 0{\cdot}001$, †$P$ *not significant* ($\chi^2$ *test*)

**Table 2** *Comparison of frequency of dissected lymph nodes and lymph node metastases in different positions for patients in Munich and Tokyo*

| | Frequency of dissected lymph nodes (%) | | | Frequency of LN metastases (%) | | |
|---|---|---|---|---|---|---|
| LN station | TU Munich ($n = 222$) | NCC Tokyo ($n = 3040$) | $P$* | TU Munich ($pN_0 = 30·2\%$) | NCC Tokyo ($pN_0 = 50·0\%$) | $P$* |
| 1 | 94·1 | 93·6 | n.s. | 35·6 | 15·6 | <0·001 |
| 2 | 96·3 | 33·8 | <0·001 | 28·8 | 6·3 | <0·001 |
| 3 | 98·4 | 97·8 | n.s | 69·3 | 34·9 | <0·001 |
| 4 | 94·3 | 96·9 | n.s. | 18·0 | 25·2 | <0·01 |
| 5 | 85·2 | 91·4 | <0·01 | 1·8 | 5·9 | <0·01 |
| 6 | 84·1 | 93·3 | <0·001 | 2·7 | 23·0 | <0·001 |
| 7 | 93·1 | 94·0 | n.s. | 22·0 | 21·8 | n.s |
| 8 | 80·4 | 88·6 | <0·001 | 12·4 | 16·4 | n.s. |
| 9 | 79·4 | 86·2 | <0·01 | 12·2 | 12·6 | n.s. |
| 10 | 78·3 | 23·7 | <0·001 | 5·4 | 5·5 | n.s |
| 11 | 79·4 | 43·9 | <0·001 | 6·3 | 6·8 | n.s. |
| 12 | 75·4 | 40·5 | <0·001 | 8·9 | 4·2 | <0·01 |
| 13 | 33·1 | 12·3 | <0·001 | 11·8 | 1·5 | <0·001 |
| 14 | 7·6 | 6·3 | n.s. | 1·8 | 2·0 | n.s |
| 15 | 3·8 | 3·0 | n.s. | 3·1 | 0·8 | <0·01 |
| 16 | 12·4 | 12·9 | n.s. | 3·9 | 4·3 | n.s. |

LN, lymph node; TU, Technical University, NCC, National Cancer Centre. *$\chi^2$ test; n.s., not significant

**Table 3** *Frequencies of lymph node metastasis with tumour in different thirds of the stomach comparison between Munich and Tokyo*

| | Upper third | | | Middle third | | | Lower third | | |
|---|---|---|---|---|---|---|---|---|---|
| LN station | TU Munich ($pN_0 = 24·1\%$) | NCC Tokyo ($pN_0 = 40·2\%$) | $P$* | TU Munich ($pN_0 = 31\%$) | NCC Tokyo ($pN_0 = 56·3\%$) | $P$* | TU Munich ($pN_0 = 36\%$) | NCC Tokyo ($pN_0 = 47·7\%$) | $P$* |
| 1 | 43·0 | 34·2 | n.s | 23·1 | 14·1 | n.s | 8·0 | 7·8 | n.s. |
| 2 | 40·1 | 21·2 | <0·001 | 17·6 | 3·9 | <0·001 | 1·3 | 1·5 | n.s. |
| 3 | 72·7 | 41·4 | <0·001 | 62·6 | 33·7 | <0·001 | 58·0 | 32·9 | <0·001 |
| 4 | 26·5 | 19·4 | n.s. | 40·7 | 25·3 | <0·01 | 28·0 | 28·0 | n.s. |
| 5 | 1·0 | 2·5 | n.s. | 2·2 | 4·6 | n.s. | 2·7 | 8·9 | n.s |
| 6 | 1·0 | 8·3 | <0·01 | 1·0 | 17·2 | <0·001 | 5·3 | 36·9 | <0·001 |
| 7 | 16·5 | 26·7 | n.s. | 17·6 | 20·4 | n.s. | 16·0 | 20·8 | n.s |
| 8 | 8·3 | 14·0 | n.s | 6·6 | 13·3 | n.s | 5·3 | 21·2 | <0·01 |
| 9 | 8·3 | 16·7 | n.s. | 9·9 | 10·8 | n.s. | 9·3 | 12·7 | n.s |
| 10 | 5·8 | 16·2 | n.s | 4·4 | 4·9 | n.s | 1·0 | 0·8 | n.s. |
| 11 | 8·3 | 14·2 | n.s. | 3·3 | 5·7 | n.s. | 2·7 | 4·4 | n.s. |
| 12 | 3·3 | 2·7 | n.s. | 11·0 | 2·6 | <0·01 | 6·7 | 6·8 | n.s. |
| 13 | 9·1 | 1·3 | <0·001 | 11·0 | 0·7 | <0·001 | 4·0 | 2·4 | n.s. |
| 14 | 2·5 | 3·0 | n.s. | 1·0 | 1·0 | n.s. | 2·7 | 2·4 | n.s |
| 15 | 1·0 | 1·5 | n.s | 1·0 | 0·4 | n.s | 1·0 | 0·8 | n.s |
| 16 | 0·8 | 6·7 | n.s | 3·3 | 3·6 | n.s | 4·0 | 3·9 | n.s |

Values are percentages. LN, lymph node; TU, Technical University; NCC, National Cancer Centre. *$\chi^2$ test; n.s., not significant

involvement for LN2, LN3 and LN13 for upper and middle thirds, but only of LN3 for lower thirds, were found in patients from TU Munich than in the Japanese study ($P < 0·001$). The situation was reversed for LN6, $P < 0·01$ (*Table 3*).

Tumours of different gastric thirds had similar frequencies of LN metastases for both populations, but along the lesser curvature (LN3) the differences were greater in all thirds ($P < 0·001$). Tumours of the upper gastric third showed more metastases at the splenic hilus and along the splenic artery in the NCC Tokyo study than TU Munich (*Table 3*).

The overall patterns and incidence of metastases were similar for both centres but at TU Munich a higher frequency of LN metastases in the retropancreatic nodes for tumours of the upper and middle third was seen ($P < 0·001$)

### *Accuracy of preoperative prediction of localization and frequency of lymph node metastases*

Only 30·1 per cent of the patients treated at TU Munich were free of LN metastases. In 18·1 per cent LN metastases were found in perigastric lymph nodes, in 27·0 per cent at node positions 1–12 and in 24·3 per cent in position 13 or higher

The program gives information on the expected frequency of metastasis in the various LN positions of patients having undergone surgery The predicted frequency of LN metastases was twice as high or greater than the real findings; in two LN positions (LN2 and LN4) false negative predictions were generated. The prediction of no metastases in LN positions was correct in 98·2 per cent of cases (*Table 4*).

For positions 13–16 a sensitivity of 100 per cent and specificity of 94·9 per cent were calculated. For lymph node areas 7–16 infiltration could also be predicted correctly. The program, by evaluation of the relevant factors, was accurate in its prediction for incidence of metastasis at positions 13–16. The validity of the program with respect to positions 1–6 was lower (*Table 5*).

## Discussion

The number of lymph nodes dissected was similar in both centres, with two differences: 33·8 per cent of the LN2 nodes were resected for patients in NCC Tokyo and 96·3 per cent in TU Munich ($P < 0.001$). The low incidence of left cardiac lymph node (LN2) dissection in Japan correlated with the low frequency of total gastrectomy. For patients with distal subtotal gastrectomy LN2 nodes were dissected only if they were suspicious. This procedure is common in Japanese centres[3,17]. The rate of dissection of retropancreatic nodes was lower at NCC Tokyo than TU Munich.

Incidence of metastases in LN1, LN2 and LN3 perigastric nodes was at least twice as high in patients from TU Munich ($P < 0.001$). The left cardiac LN position was more frequently involved with metastases in patients at TU Munich than NCC Tokyo This may be related to a higher incidence of tumours in the upper third in TU Munich (43·2 per cent) compared with NCC Tokyo (19·2 per cent) ($P < 0.01$). Concerning the tumours of the middle and upper third, patients at TU Munich had more metastases in node stations 12 and 13 than did patients in NCC Tokyo.

For all node positions the predicted frequency of LN metastasis was double or more the actual frequency. There were very few false negatives but many false positive predictions. The data do not demonstrate significant differences between the frequency of dissection and the predicted rate in stages of positions 1–6; for positions 10, 14, 15 and 16 the rate of dissection is lower than the rate of prediction. The number of false positives due to incomplete resection is unknown, as is the number of unnecessarily resected lymph nodes due to positive prediction.

**Table 4** *Lymph node metastases for patients with gastric cancer in the Technical University of Munich: frequency of prediction of no metastases (percentage) and number of false negative predictions*

| LN station | No metastases prediction | False negative predictions (*n*) |
|---|---|---|
| 1 | 13·7 | 0 |
| 2 | 37·5 | 3 |
| 3 | 12·7 | 0 |
| 4 | 23·2 | 1 |
| 5 | 53·8 | 0 |
| 6 | 19·0 | 0 |
| 7 | 17·3 | 0 |
| 8 | 23·9 | 0 |
| 9 | 21·0 | 0 |
| 10 | 66·6 | 0 |
| 11 | 42·0 | 0 |
| 12 | 53·7 | 0 |
| 13 | 73·1 | 0 |
| 14 | 69·9 | 0 |
| 15 | 75·2 | 0 |
| 16 | 51·0 | 0 |

LN, lymph node

The most important measure of the validity of this method is the negative predictive value, which indicates the number of patients with unpredicted LN metastases found on surgical exploration, i.e. the number of patients who would undergo inadequate lymphadenectomy if the extent of their surgery was based on computer prediction alone. In our series, this would have occurred in only four (1·8 per cent) patients (*Table 4*). It has been shown that the evaluation of LN metastases in the different positions using the Maruyama program is a very accurate method.

The Maruyama program was developed using data collected after operation. Analysis of parameters such as depth of infiltration, number of infiltrated lymph nodes, histology etc. was helpful in developing an effective program. To apply this method after operation with the same accuracy, the same information needs to be available. Other information is also essential: sex and age are obvious; endoscopy provides reliable data about the type, Borrmann classification and site and size of the tumour; histology can be determined assuming that the biopsy is representative; it remains difficult to obtain reliable information about the depth of infiltration (pT); endosonography achieves accuracy of up to 82 per cent in terms of T stage prediction[18].

### *Clinical relevance of the exact prediction of lymph node metastases*

Only patients with few LN metastases benefit from standard lymphadenectomy of positions 1–12[15,19–22]. After extended LN dissection morbidity (pancreatic fistula, abdominal infection, rebleeding etc.) rises. In TU Munich the morbidity but not the mortality rate increased following more radical lymphadenectomy[23]. Other studies confirm this[17,24] The LN dissection will not be very effective for palliative resections ($R_1$ or $R_2$)[2,15,25,26].

## Acknowledgements

The authors are grateful to T. Hahne for collection and evaluation of these data

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**Table 5** *Validity of computerized prediction of lymph node metastases in different positions for patients at the Technical University of Munich*

| Lymph node station | Sensitivity (%) | Specificity (%) | Positive predictive value (%) | Negative predictive value (%) | Accuracy (%) |
|---|---|---|---|---|---|
| 13–16 | 100 | 95 | 86 | 100 | 96 |
| 7–12 | 100 | 78 | 83 | 100 | 89 |
| 1–6 | 97 | 43 | 80 | 94 | 82 |

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# Oesophagitis and pH of refluxate: an experimental and clinical study

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*This experimental and clinical study examined the relationship between oesophageal damage and optimal pH of refluxate, and whether 24-h pH monitoring at optimal pH could discriminate the severity of oesophagitis. The rabbit oesophagus was perfused* in vivo *with pepsin and hydrochloric acid solutions of differing pH for 60 min. Maximal oesophageal damage coincided with peptic solutions at pH 1·5–2·5. Fifty-nine patients with proven gastro-oesophageal reflux disorders were tested for manometric features of the lower oesophageal sphincter (pressure, overall length and abdominal length) and oesophageal exposure to different pH levels. They were classified into four groups according to the endoscopically demonstrated severity of oesophagitis. Supine exposure at the optimal pH level for pepsin activity (pH 1·5–2·5) and overall sphincter length were found to discriminate the severity of oesophagitis reliably in 75 per cent of cases.*

The most frequent cause of oesophagitis is abnormal exposure to gastrointestinal contents, mainly acid and pepsin, due to an incompetent lower oesophageal sphincter. Patients with inflammation of the distal oesophagus have increased exposure to acid reflux compared with healthy individuals as assessed by 24-h pH monitoring[1,2]. Oesophagitis improves when acid and pepsin secretion is inhibited pharmacologically or when the competency of the cardia is surgically restored[3,4]. However, oesophagitis develops in about half the patients with proven gastro-oesophageal reflux[5,6], as defined by abnormal exposure to pH < 4 with 24-h pH monitoring. Patients with differing severity of oesophagitis cannot be separated on the basis of 24-h pH monitoring[7,8]. Possible explanations for this include variability in the defensive capacity of the gullet (motility, saliva outflow and composition, and oesophageal epithelial resistance) or differences in the composition of the refluxed juice (concentration of hydrogen ions or presence of bile and pancreatic proteolytic enzymes).

This study therefore examined the relationship between oesophageal damage and the optimal pH of the refluxate and, in particular, whether the severity of oesphagitis can be determined using a different pH threshold in the 24-h oesophageal pH monitoring test

One experimental and one clinical study were designed (studies A and B) as follows.

## Study A: Materials and methods

The objective of the study was to evaluate the relationship between acid and pepsin using oesophageal mucosa in an *in vivo* model.

New Zealand white rabbits (1–3 kg body-weight) were anaesthetized with ketamine (8 mg/kg). An incision was made in the neck, the cervical oesophagus was dissected and a silicone tube (4 mm internal diameter) was inserted into the oesophagus Through an abdominal incision, the oesophagus was cannulated at the level of the oesophagogastric junction. Watertight seals were maintained around these catheters with umbilical tape A segment of the oesophagus 5–7 cm in length was perfused isolated from the rest of the gastrointestinal tract[9]. The perfusion rate was 40 ml/min, initially with saline (10 min) and then with isotonic solutions of varying pH containing pepsin at various concentrations (60 min) (*Table 1*) At the end of the experiment, the rabbits were killed and the oesophagus removed and fixed in 10 per cent buffered formalin Histopathology was performed on the proximal, central and distal portions of the oesophagus after staining with haematoxylin and eosin.

Epithelial damage (superficial, moderate and deep erosions and ulcers), intraepithelial oedema and inflammation, subepithelial oedema, inflammation and angiectasis were considered separately. Each of these parameters was graded from zero to 3 and the final score was the sum of all scores.

The maximum score was given when ulceration of the whole mucosa was observed The Mann–Whitney $U$ test was used for statistical analysis.

## Study A: Results

Either no or minimal oesophageal damage (score less than 8) was observed when the oesophagus was perfused with solutions without pepsin. Mucosal lesions scoring more than 8 were observed only when the oesophagus was perfused with pepsin solutions at pH $\leqslant 3$, whereas damage was minimal or absent with solutions at pH 4.

In general, damage increased with increasing concentrations of pepsin. No significant differences in mucosal damage were observed when the oesophagus was perfused with pepsin solutions at pH 2·5, 2·0 or 1·5 Mucosal damage scores obtained with solutions at pH 1·5, 2·0 and 2·5 were significantly greater than those obtained at pH 3 (*Figure 1*)

## Study B: Patients and methods

In view of the results of study A, the clinical study was designed to verify whether a defective oesophageal sphincter (as defined by manometry) and acid exposure of the distal oesophagus at the optimal pH level for pepsin activity (pH 2·5–1·5) would determine the severity of oesophagitis in patients with gastro-oesophageal reflux disease

### *Patients*

The study involved 59 symptomatic patients with abnormal acid exposure in the distal oesophagus proven by 24-h pH monitoring.

**Table 1** *Different solutions for the perfusion of rabbit oesophagus*

| | pH of 0·3 N HCl | | | | |
|---|---|---|---|---|---|
| | 1·5 | 2 | 2·5 | 3 | 4 |
| Pepsin (mg/ml) | 0·0 | 0·0 | 0·0 | 0·0 | 0·0 |
| | 0·1 | 0·1 | 0·1 | 0·1 | 0·1 |
| | 0·3 | 0·3 | 0·3 | 0·3 | 0·3 |
| | 0·6 | 0·6 | 0·6 | 0·6 | 0·6 |

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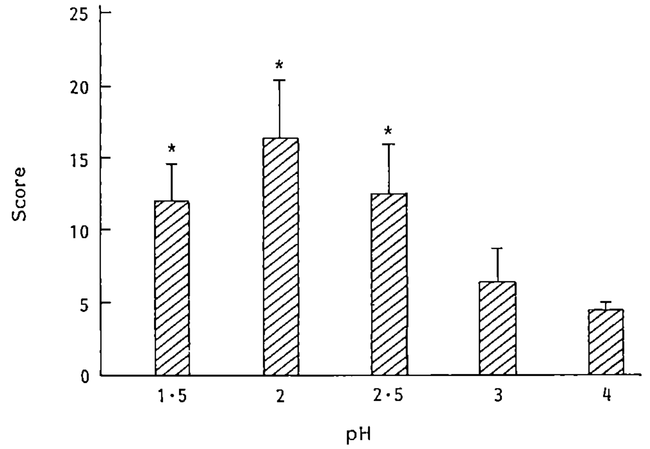

**Figure 1** *Score of oesophageal mucosa lesion after 60 min perfusion of rabbit oesophagus with solutions containing pepsin* (*0·1, 0·3 and 0·6 mg/ml*) *at different pH. Values are mean(s.e.m.) of six measurements performed on two animals for each pepsin concentration.* **Statistically different* (P < 0·05, *Mann–Whitney* U *test*) *from pH 3*

Patients who had undergone previous biliary, gastric or oesophageal surgery, or who had primary oesophageal motor disorders or collagen diseases, were excluded. Patients were divided into four groups according to the severity of oesophageal injury as assessed by endoscopy. The Savary–Miller[10] classification of oesophagitis was adopted. Group 1 consisted of 17 patients with uncomplicated gastro-oesophageal reflux disease, i.e. absence of oesophagitis (six women, 11 men; median age 44, range 17–75 years). Group 2 consisted of 17 patients with grade 1 oesophagitis, i.e. redness of the mucosa and/or linear erosions (five women, 12 men; median age 47, range 21–72 years). Group 3 consisted of 12 patients with grade 2 oesophagitis, i.e. confluent erosion not covering the entire circumference of the oesophagus (two women, ten men, median age 59, range 24–72 years). Group 4 consisted of seven patients with grade 3 or grade 4 oesophagitis (i.e. erosive or exudative lesions covering the entire circumference of the oesophagus or the presence of ulcers or stricture) and six patients with histologically proven columnar lined epithelium in the oesophagus covering more than 3 cm above the cardia (Barrett's oesophagus), a total of 13 patients (four women, nine men; median age 61, range 35–74 years). All endoscopies were performed in the same laboratory and the duration of each patient's symptoms was recorded.

Fifteen asymptomatic volunteers (six women, nine men, median age 25, range 20–80 years) were used as a control group, and underwent oesophageal manometry and 24-h pH monitoring.

### *Oesophageal manometry*

Manometry was performed using a single catheter assembly consisting of seven tubes bonded together. Four distal openings were placed at the same level, 90° from each other; three more openings were placed 5 cm apart, 120° from each other. The tubes were perfused via a hydropneumatic pump (Mui, Ontario, Canada) at a rate of 0·8 ml/min. Each tube was connected to an external transducer (Statham P23XL, Spectramed, Bilthoven, Netherlands) positioned at the midaxillary level. A belt pneumograph was positioned around the chest to record respiratory excursions. Pressures were recorded, processed and printed using a computerized manometric system (Dyno System, Menfis, Bologna, Italy)[11]. Manometry was performed with subjects in a fasting state, all medications having been discontinued 24 h before the test. Withdrawal of the catheter into the oesophagus was performed at a velocity of 1 mm/s using an automatic motorized retractor. Three manometric characteristics of the distal oesophageal sphincter were measured: sphincter pressure, abdominal length and overall length. The end-expiratory gastric baseline was used as a zero reference for pressure measurement. A persistent rise in pressure exceeding 2 mmHg above the gastric baseline marked the distal border of the sphincter. The proximal border was marked by the point where the sphincter pressure dropped to the end-inspiratory oesophageal baseline pressure. At least seven measurements of the distance between these two points were made, and the mean was taken to represent the overall length of the sphincter. The point at which the end-inspiratory pressure changed from positive to negative represented the respiratory inversion point. At least seven measurements of the distance between this point and the distal border of the sphincter were made, and the mean was taken to represent the abdominal length of the sphincter.

Sphincter amplitude was measured as the difference (in millimetres of mercury) between the gastric baseline and the pressure at the respiratory inversion point in the middle of the respiratory cycle. At least seven measurements of sphincter pressure were obtained, and the mean was used to compensate for changes of pressure at each orifice due to radial asymmetry of the sphincter[12].

### *Oesophageal pH monitoring*

Twenty-four-hour pH monitoring (8-s interval samples) of the distal oesophagus was carried out using glass electrodes with internal reference (440 M4, Ingold, Urdorf, Switzerland) and a portable solid-state monitor (Proxima 2, Synectics, Stockholm, Sweden).

The probe was calibrated in a standard buffer solution at pH 7 and 2 (9439 and 9433, Merck, Darmstadt, Germany) before and after monitoring. The pH probe was passed transnasally and positioned 5 cm above the upper border of the sphincter, as determined by prior manometry. Subjects were then instructed to avoid strenuous exertion and to remain in the upright or sitting position during the day, until they retired in the evening. The period of time in the supine position (automatically recorded by the data logger) was assumed to be for sleep. Subjects also followed a strict diet, being allowed food with a pH between 5 and 7 for three meals. Only water was permitted between meals. A diary was kept of food and fluid intake, and symptoms. At the end of the recording period, the data were transferred to a personal computer and analysed using a commercial software program. When the pH dropped to <4, subjects were classified as having gastro-oesophageal reflux and the following parameters were considered: total time of acid reflux and acid exposure during supine and upright periods (as a percentage of recorded time), total number of acid reflux episodes, number of episodes lasting 5 min or more, and duration of the longest episode of acid reflux[13]. Patients were considered to have abnormal acid exposure of the distal oesophagus when two or more of these parameters exceeded the mean plus 2 s.d. of controls. The time of acid exposure was then separately considered for each of the pH intervals 4–3, 3–2, 2·5–1·5, 2–1 and 1–0, for which the above-mentioned parameters were then calculated, as for the interval 4–0.

### *Statistics*

Data are expressed as mean(s.e.m.). A commercial statistical package (SAS/STAT, SAS Institute, Cary, North Carolina, USA) was used for the analyses.

One-way analysis of variance (ANOVA) and Scheffé's test[14] were used to compare the four groups.

### *Discriminant analysis*

To obtain reliable statistical results, discriminant analysis was performed considering only two groups of patients, i.e. those with no or mild oesophageal lesions (groups 1 and 2) and those with severe lesions, complications or Barrett's oesophagus (groups 3 and 4), considering the high number of variables (42) in comparison with the relatively low number of observations (59). The stepwise regression test was applied to the original 42 variables (age, body-weight, duration of symptoms, lower oesophageal sphincter pressure, overall and abdominal length of lower oesophageal sphincter, all the DeMeester parameters for each pH interval). Eight variables were found to be significant ($r^2 = 0·35$, $\alpha$ level = 10 per cent) (*Tables 2* and *3*). A linear model of discriminant analysis was then applied to these eight variables[15].

**Table 2** *Results of the stepwise regression test applied to the 42 original variables of 24-h pH monitoring and manometry*

| | | $r^2$ | $P > F$ |
|---|---|---|---|
| 1 | Percentage exposure in supine position at pH 2·5–1·5 | 0·34 | 0·0001 |
| 2 | Overall length of lower oesophageal sphincter | 0·34 | 0·0001 |
| 3 | Lower oesophageal sphincter pressure | 0·17 | 0·02 |
| 4 | Number of reflux episodes at pH 4–3 | 0·08 | 0·05 |
| 5 | Number of reflux episodes at pH 4–3 lasting >5 min | 0·10 | 0·02 |
| 6 | Number of reflux episodes at pH 3–2 lasting >5 min | 0·21 | 0·05 |
| 7 | Number of reflux episodes at pH 3–2 | 0·06 | 0·05 |
| 8 | Number of reflux episodes at pH 2·5–1·5 | 0·02 | 0·05 |

**Table 3** *Results of discriminant analysis (linear model) subsequently applied to the eight variables selected*

| | Mean correct classification |
|---|---|
| All eight variables | 0·76 |
| Percentage exposure in supine position at pH 2·5–1·5 | 0·66 |
| Overall length of lower oesophageal sphincter | 0·66 |
| Percentage exposure in supine position at pH 2·5–1·5 and overall length of lower oesophageal sphincter | 0·75 |

**Table 4** *Manometric characteristics of the lower oesophageal sphincter and acid exposure in the distal oesophagus in the control group*

| | Mean(s.e.m.) |
|---|---|
| Lower oesophageal sphincter | |
| Pressure (mmHg) | 17·7(1·4) |
| Overall length (mm) | 40·4(1·9) |
| Abdominal length (mm) | 25·8(1·5) |
| Percentage of total time at pH <4 | 1·13(0·3) |
| Percentage of supine time at pH <4 | 0·4(0·3) |
| Percentage of upright time at pH <4 | 1·75(0·5) |
| Number of reflux episodes | 19·3(3·1) |
| Number of reflux episodes >5 min | 0·86(0·5) |
| Duration of longest reflux episode (min) | 5·1(1·8) |

**Table 5** *Duration of symptoms in patients with gastro-oesophageal reflux disease*

| Group | Degree of oesophagitis | Duration of symptoms (months) |
|---|---|---|
| 1 | No oesophagitis | 53·5(12·9) |
| 2 | Hyperaemia or linear erosion (grade 1) | 37·6(10·2) |
| 3 | Confluent erosion not covering entire circumference (grade 2) | 68·7(27·5) |
| 4 | Erosions covering entire circumference (grade 3), or ulcer, stricture or Barrett's epithelium (grade 4) | 48·0(11·7) |

Values are mean(s.e.m.)

## Study B: Results

The manometric lower oesophageal sphincter measurements and pH values of the control group are reported in *Table 4*.

No differences were observed in age distribution or duration of symptoms in the four groups (*Table 5*). Patients with severe injuries of the oesophageal mucosa (group 4) had a significantly lower sphincter pressure compared with those without mucosal lesions (group 1). Moreover, they had a significantly shorter sphincter (both overall and abdominal lengths) compared with all other groups (*Figures 2* and *3*).

Total and supine acid exposure of the distal oesophagus to a pH <4 was significantly increased in patients with severe lesions or complications (group 4) compared with patients with no or minimal lesions (groups 1 and 2). No significant differences were found between groups 3 and 4 (*Figure 4*). Total and supine exposure at the optimum pH for pepsin activity (pH 2·5–1·5) was significantly different in patients with severe mucosal injury compared with all other groups (*Figure 5*).

### *Discriminant analysis*

The stepwise regression test had identified eight patient-discriminating variables (*Table 2*). The discriminant analysis test was applied to these variables and gave rise to an accuracy of 76 per cent. When considered separately, the percentage of acid exposure in the supine position at pH 2·5–1·5 and the overall length of sphincter were both found to have a power of correct classification of 66 per cent. Taken together, these two variables gave a correct classification in 75 per cent of cases, which means that they alone have 98 per cent of the discriminant ability of all eight original variables.

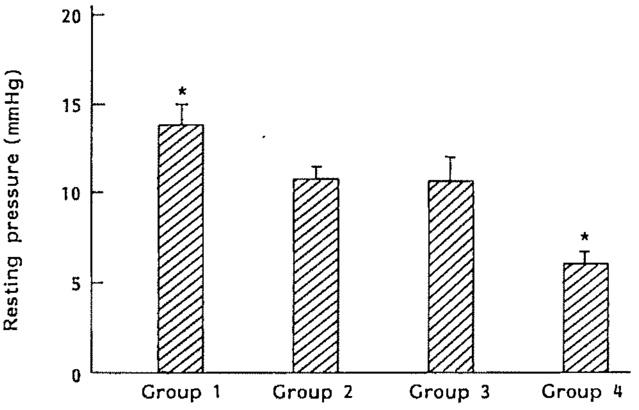

**Figure 2** *Mean(s.e.m.) resting pressure of the lower oesophageal sphincter in patients with increasing severity of oesophagitis. *Patients with severe mucosal injury (group 4) had a significantly lower resting pressure compared with those without lesions (group 1,* P *< 0·05, ANOVA and Scheffé's test)*

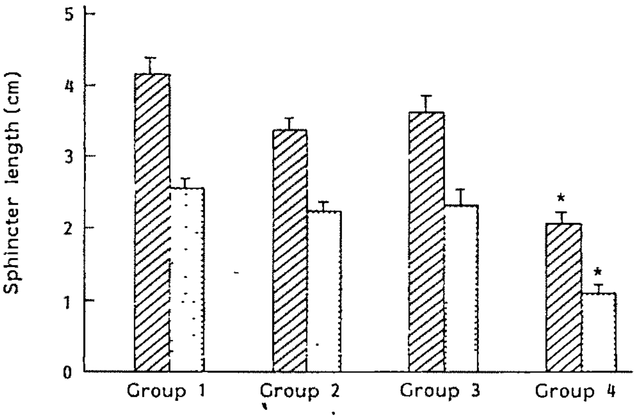

**Figure 3** *Lower oesophageal sphincter mean(s.e.m.) overall (▨) and mean(s.e.m.) abdominal (☐) length in patients with increasing severity of oesophagitis. *Patients with severe mucosal lesions (group 4) had a statistically shorter sphincter (both abdominal and overall length) compared with all other groups* (P *< 0·05, ANOVA and Scheffé's test)*

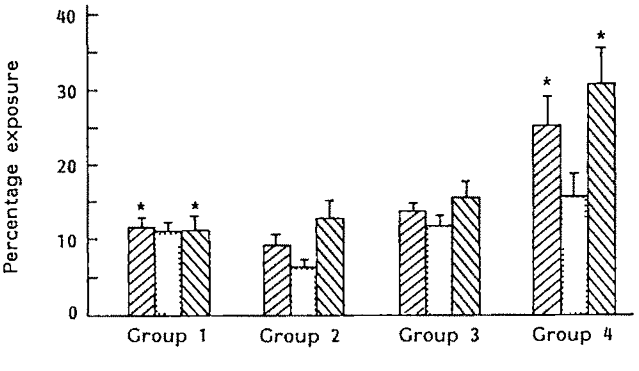

**Figure 4** *Mean(s.e.m.) exposure of distal oesophagus to gastric juice at pH < 4 ▨, total, ☐, upright, ▧, supine *Patients with severe mucosal injury (group 4) had a significantly greater total and supine exposure compared with those without lesions (group 1,* P *< 0·05, ANOVA and Scheffé's test)*

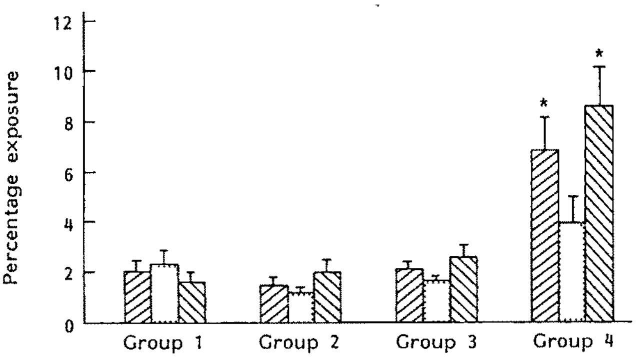

**Figure 5** *Mean(s e m.) exposure of distal oesophagus to gastric juice at pH 2·5–1·5 ▨, total; ☐, upright, ▧, supine *Patients with severe mucosal injury (group 4) had a significantly greater total and supine exposure compared with all other groups* (P < 0·05, *ANOVA and Scheffé's test*)

## Discussion

In 1974 Johnson and DeMeester[13,16] defined gastro-oesophageal reflux as any drop of the oesophageal pH below 4, on the basis of various pH tests[17,18], giving the best discrimination between asymptomatic controls and patients. Oesophageal pH monitoring is now accepted as the most sensitive test to detect abnormal gastro-oesophageal reflux. However, the test usually fails to discriminate between different degrees of severity of oesophagitis. Twenty-four-hour pH tests enable a semiquantitative analysis of hydrogen ion concentration, and other substances such as bile and pancreatic juices cannot be detected.

Current pH data loggers allow for sophisticated computer analysis, and pH thresholds other than pH <4 may be investigated.

The proteolytic activity of pepsin, assumed to be the most probable cause of lesions of the oesophageal mucosa, is strictly dependent on hydrogen ion concentration in the medium. A detailed analysis of oesophageal exposure at different pH thresholds was constructed to discriminate patients with different degrees of oesophagitis. Previous experiments have shown that the optimum pH for pepsin-catalysed reactions is between 1·5 and 2·5 *in vitro*. A lower pH (1·5) is required when the whole oesophageal mucosa is used as a substrate *in vivo*[18–20]. The experimental study, confirmed that the most severe injury to rabbit oesophageal mucosa was obtained at pH between 2·5 and 1·5. At pH 3 the enzymatic activity of pepsin was still present but damage to the mucosa was reduced, indicating that exposure at pH 2·5–1·5 is crucial to the induction of mucosal injuries.

These observations were supported by the clinical study; exposure at pH 2·5–1·5 in the supine position was able to discriminate among groups of patients with different degrees of oesophagitis.

The importance of reflux in causing oesophagitis when the patient is recumbent (assuming that it occurs during sleep) is emphasized in many studies and probably reflects reduced peristaltic and clearing activity of the oesophagus when the subject is asleep[21].

The other discriminating parameter that emerged from the analysis was the overall length of the lower oesophageal sphincter. Progressive shortening of the sphincter with increasing severity of oesophagitis has already been reported[2]. Whether this is a cause of the disease or a consequence of peptic damage is controversial. Patients with a short sphincter and increased acid exposure at pH 2·5–1·5 should be considered as high-risk subjects prone to develop oesophagitis and suitable for treatment with aggressive medical or surgical therapy.

In conclusion, this study supports the hypothesis that severe oesophagitis is caused by prolonged contact of pepsin with the oesophageal mucosa in a low-pH environment. Acid exposure at a pH of 2·5–1·5 in the supine position associated with a defective lower oesophageal sphincter may be used to discriminate patients with varying degrees of oesophagitis.

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# Muscle strength is improved after parathyroidectomy in patients with primary hyperparathyroidism

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*Fatigue and muscular weakness are prevalent symptoms in patients with primary hyperparathyroidism. This study examined muscular strength before and after operation in a group of eight patients with hyperparathyroidism and in a control group of seven patients with benign thyroid lesions. The maximum power grip, pronation and supination, and endurance for the same muscular movements, were studied by means of a computer program. Patients with hyperparathyroidism had impaired muscular strength compared with the controls but 12 months after operation a significant improvement of all muscular performance was observed. No such improvement was detectable among the controls. There was no correlation between the levels of serum calcium and parathyroid hormone and the measurements recorded before and after operation. Muscular impairment in hyperparathyroidism is measurable by an objective technique. Improvement occurs after surgery.*

Fatigue and muscular weakness are symptoms commonly encountered in patients with primary hyperparathyroidism, and most improve after surgery[1–3]. Many patients are asymptomatic but seem to 'improve' after surgery[4–6]. Whether patients without typical symptoms of hyperparathyroidism should be operated on or not is a matter of debate[7].

Objective assessment of muscular function before and after operation in patients with hyperparathyroidism has been studied, confirming the clinical impression of postoperative improvement of muscular capacity. The strength/power of quadriceps and the respiratory muscle groups improves after correction of hypercalcaemia[4–6,8].

Measurements of grip flexion, pronation and supination have proved valuable in assessing maximal muscular strength and endurance of the hand after surgery. In the present study the application of such measurements was used to evaluate muscle strength before and after parathyroidectomy.

## Patients and methods

Eight patients with suspected primary hyperparathyroidism (six women, two men, median age 53 years) and seven patients with benign thyroid lesions (six women, one man; median age 56 years) were studied. All patients were free from known neuromuscular disorders, diabetes and previous wrist fractures, and none had undergone surgery to their dominant hand. Clinical and biochemical data for the patients suffering from primary hyperparathyroidism are presented in *Table 1*.

Investigations were carried out before operation and 12 months after operation. All patients with hypercalcaemia had a parathyroid adenoma removed and became normocalcaemic. No patient received calcium and/or vitamin D therapy at follow-up. Those with benign thyroid lesions underwent hemithyroidectomy and were normocalcaemic and euthyroid at follow-up. No patient was on any continuous muscle training programme before or after operation.

The isometric muscle strength in the dominant hand was studied, by the same physiotherapist on both occasions, by means of an IBM-compatible personal computer-based program, HASTRAS (Hand Strength Analysis System), developed at the University Hospital of Umeå. This program measures the maximal grip strength (power, pinch, key, press) and torque, as well as endurance after maximally applied strength during 30 s and motor skills. Strain-gauge transducers were adjustable to accommodate different hand sizes. Curves and relevant parameters were determined with adapted electronics. All data were stored for later statistical processing.

Hand strength was measured in a standardized position, the patient was seated with the shoulder adducted and neutrally rotated, the elbow flexed at 90° and the forearm in neutral position, and the wrist positioned at 0–30° dorsiflexion and between 0 and 15° of ulnar deviation. Maximal voluntary power grip, maximal pronation and supination (peak torque) were measured in newtons (N). Endurance during the same manoeuvres (30 s) was measured in newton seconds

**Table 1** *Preoperative clinical and biochemical data in eight patients with primary hyperparathyroidism*

| Patient no. | Sex | Age (years) | Muscle symptoms | Serum calcium* (mmol/l) (2·10–2·60) | Ionized calcium* (mmol/l) (1·14–1·29) | Serum phosphate* (mmol/l) (0·82–1·50) | Serum parathyroid hormone* (pg/l) (<10) |
|---|---|---|---|---|---|---|---|
| 1 | F | 50 | Yes | 2·70 | 1·30 | 0·80 | 4·2 |
| 2 | F | 44 | Yes | 2·84 | 1·37 | 0·58 | 10·0 |
| 3 | F | 55 | Yes | 2·90 | 1·31 | 0·90 | 67·0 |
| 4 | F | 40 | Yes | 2·76 | 1·50 | 0·53 | 15·0 |
| 5 | M | 58 | Yes | 2·87 | 1·43 | 0·64 | 1·4 |
| 6 | M | 36 | Yes | 2·76 | 1·31 | 0·88 | 8·1 |
| 7 | F | 60 | Yes | 2·90 | 1·40 | 0·78 | 5·2 |
| 8 | F | 57 | Yes | 2·85 | 1·39 | 0·82 | 16·4 |
| Median |  | 53 |  | 2·85 | 1·38 | 0·79 | 13·0 |

*Normal ranges are given in parentheses

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(Ns) Values reported were the mean of at least three different measurements.

Statistical significance was assessed by means of Student's *t* test for paired samples, and correlations were calculated with Pearson's correlation coefficient

## Results

The individual results for maximum power grip, supination, pronation and endurance before and after operation are shown in *Figures 1–6*.

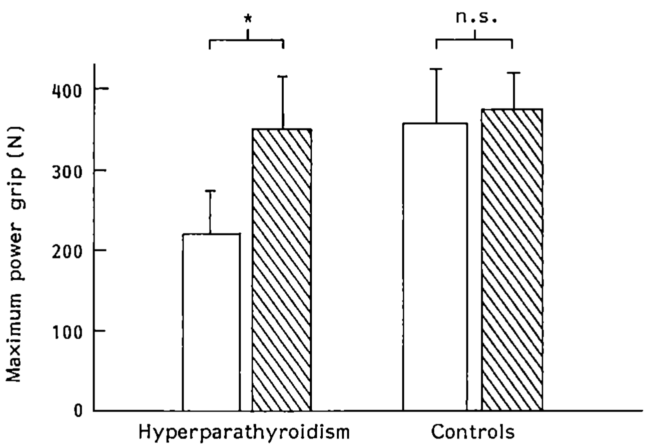

**Figure 1** *Maximum power grip before (□) and after (▨) operation in eight patients with primary hyperparathyroidism and seven controls with benign thyroid lesions Values are mean(s.e m ) *$P < 0{\cdot}008$ (Student's* t *test), n.s., no significant difference*

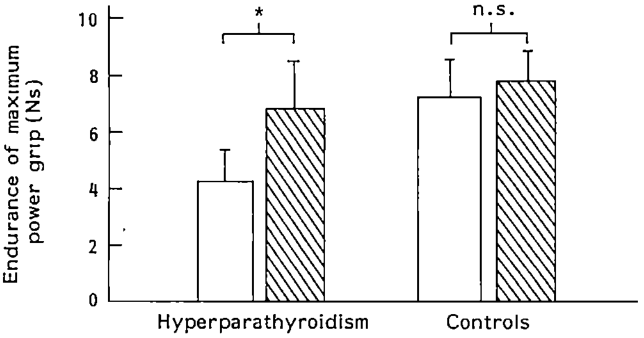

**Figure 2** *Endurance of maximum power grip before (□) and after (▨) operation in eight patients with primary hyperparathyroidism and seven controls with benign thyroid lesions Values are mean(s e.m.) *$P < 0{\cdot}002$ (Student's* t *test), n.s , no significant difference*

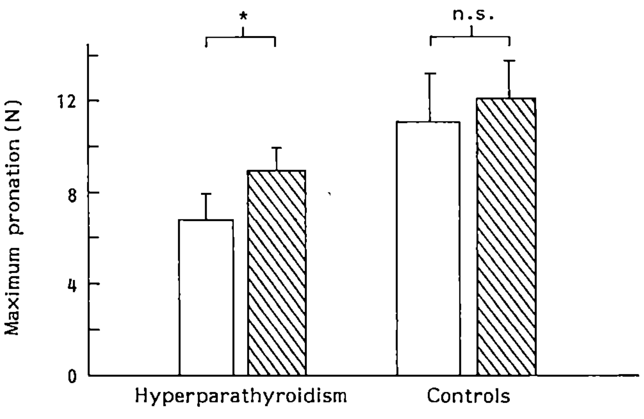

**Figure 3** *Maximum pronation before (□) and after (▨) operation in eight patients with primary hyperparathyroidism and seven controls with benign thyroid lesions Values are mean(s e m ) *$P < 0{\cdot}001$ (Student's* t *test), n.s , no significant difference*

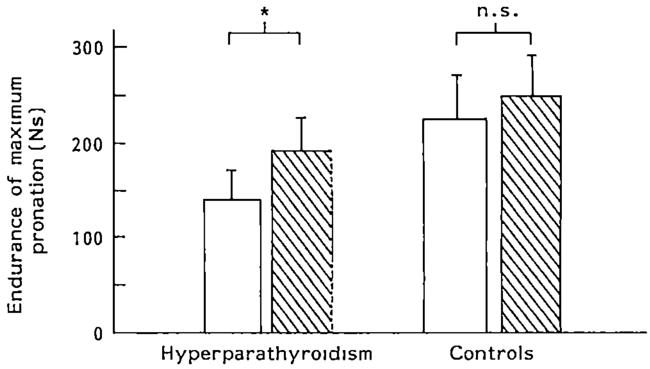

**Figure 4** *Endurance of maximum pronation before (□) and after (▨) operation in eight patients with primary hyperparathyroidism and seven controls with benign thyroid lesions Values are mean(s.e.m ) *$P < 0{\cdot}002$ (Student's* t *test), n s , no significant difference*

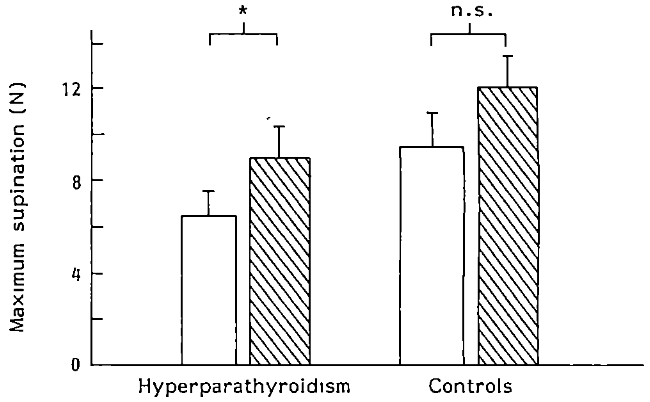

**Figure 5** *Maximum supination before (□) and after (▨) operation in eight patients with primary hyperparathyroidism and seven controls with benign thyroid lesions Values are mean(s.e.m ) *$P < 0{\cdot}03$ (Student's* t *test), n.s , no significant difference*

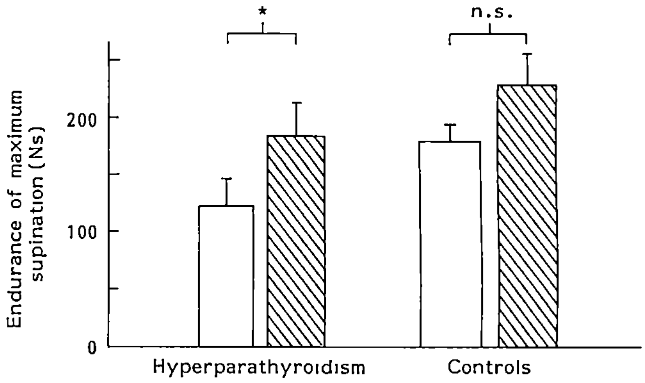

**Figure 6** *Endurance of maximum supination before (□) and after (▨) operation in eight patients with primary hyperparathyroidism and seven controls with benign thyroid lesions. Values are mean(s.e.m.). *$P < 0{\cdot}03$ (Student's* t *test), n.s , no significant difference*

Before operation, patients with primary hyperparathyroidism had a significantly depressed muscular capacity compared with the control group. The maximum power grip increased after operation in the hyperparathyroidism group ($P < 0{\cdot}008$) but was unchanged in the control group (*Figure 1*). Individual improvements were registered in seven of eight patients. Endurance for maximal power grip was improved in all patients with hyperparathyroidism and for the whole group a significant improvement was registered ($P < 0{\cdot}002$). Power grip endurance was unchanged for the controls (*Figure 2*).

Maximal pronation in the hyperparathyroidism group increased significantly ($P < 0{\cdot}001$) but was unchanged among the controls (*Figure 3*). Individual improvements were registered in seven patients. Endurance for maximal pronation increased in all patients with hyperparathyroidism and for the whole group a significant improvement was noted ($P < 0\cdot002$). No significant change occurred in the control group (*Figure 4*).

The maximal supination increased in the hyperparathyroidism group ($P < 0\cdot03$), with individual improvements in all but one patient. No significant change took place in the control group (*Figure 5*). Endurance for maximal supination increased significantly ($P < 0\cdot03$) with individual improvements in six of eight patients with hyperparathyroidism. The controls were unchanged (*Figure 6*).

There was no correlation between the levels of serum calcium and parathyroid hormone and preoperative muscular capacity or postoperative improvements. There was no obvious relation between the patients' muscular symptoms before operation and the measurements recorded on the different tests before or after operation. There was no correlation between the symptoms and the level of serum calcium.

## Discussion

Primary hyperparathyroidism is diagnosed more frequently today. Many patients are asymptomatic[4,5] and some present with subjective muscle disorders[1,9–12]. In this series, all patients had complaints of impaired muscular capacity.

Neuromuscular symptoms in hyperparathyroidism were classically defined in terms of fatigue, proximal muscle weakness and muscle atrophy[13,14], and abnormal findings have been registered on various neurophysiological tests[13]. During the past decade objective, quantitative attempts have been made to show that muscle function improves after the correction of hypercalcaemia[4–6,8]. Hedman *et al.*[4] and Wersäll-Robertson *et al.*[5] did not compare preoperative muscle capacity with controls but in a previous study they observed that a decreased muscle capacity was present in patients with hyperparathyroidism[8]. Joborn *et al.*[6] failed to demonstrate any impairment of muscle force in distinction to the results of this study. One explanation might be the difference in subjective muscle symptoms (100 per cent in this study compared with 25 per cent in that of Joborn *et al.*[6]).

This investigation studied peak muscle torque and endurance in a group of patients suffering from hyperparathyroidism or benign thyroid lesions before and after surgery. The isokinetic muscle torque method is appropriate for tests before and after training, and is dependent on the skill and cooperation of the person being tested. The simplicity of an isometric muscle torque test using ordinary hand grips does not require this level of cooperation and understanding. More important is the posture of the hand because the amount of force exerted by the muscles on the tendons and fingers and, as a result, on the hand is much stronger is some positions than in others. The use of the elbow-flexed position in standardized grip evaluations results in a significantly stronger grip strength than in the fully extended position[15]. No significant differences in grip strength with the wrist positioned at 0–30° dorsiflexion and 0–15° ulnar deviation have been reported[16,17].

The present study demonstrates the improvement of muscular peak torque and muscular endurance by isometric tests of maximal power grip, pronation and supination, confirming that it is possible to measure objectively muscular impairment in patients with hyperparathyroidism. Objective improvements are documented after successful parathyroid surgery.

The only previous study using an isometric test procedure with postoperative improvements was work in this hospital on maximal end-expiratory and inspiratory pressures studying respiratory muscle strength[8]. Hedman and colleagues[4] did not find any improvement in isometric muscle strength, merely an isokinetic increase.

The majority of the patients in this study had subjective muscle symptoms but there was no correlation between the degree of impairment before operation and the degree of improvement after operation. There was no correlation between the level of serum calcium before operation and the degree of improvement – a similar finding to that of others[5,8] but contrary to two recent reports[6,7].

The physiological functions of extracellular and intracellular calcium have been understood for more than 100 years[18], but the exact role of an excess of calcium and/or parathyroid hormone has not been clearly defined. Garber[19] showed that parathyroid hormone releases amino acids from skeletal muscle and Goldstein and Massry[20] demonstrated that excess parathyroid hormone impedes conduction velocity in certain motor neurones.

Muscle atrophy and abnormal electromyographic findings previously reported are not generally found among patients with hyperparathyroidism today[13,21].

Hypercalcaemia frequently manifests as pronounced fatigue with psychiatric symptoms which are reversible after surgery[22,23]. This improvement may contribute to improved muscular performance on different tests where the patient's cooperation is a prerequisite. This general improvement of the patient's health after operation might be more important than the restitution of normal neurophysiological transmission. Improving muscle strength in these patients may improve their quality of life.

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# Case report

**Br. J. Surg. 1992, Vol. 79, February, 168**

## Adjuvant herbal treatment for gallstones

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The last few years have seen an explosion in therapeutic options for symptomatic gallstones. Non-operative methods such as ultrasonic lithotripsy use adjuvant gallstone dissolution therapy for extended periods, and oral gallstone dissolution therapy often requires 2 years of treatment Gallstones are also treated by practitioners of alternative medicine, and their experience may find application in conventional surgical practice.

### Case report

A 48-year-old man was admitted for cholecystectomy with the following history. In 1988 he had suffered an attack of biliary colic after a fish supper, after which he became jaundiced. The jaundice resolved and ultrasonography confirmed multiple gallstones After waiting for some months for a surgical opinion, he sought remedy from a practitioner of herbal cures For a modest sum, he was given the following advice: he should procure a pint of olive oil and ten fresh lemons; after a 12-h fast, he should take 4 tablespoons of olive oil followed by 1 tablespoon of lemon juice by mouth every 15 min and continue until the olive oil was finished. This the patient did between 19 00 hours and 22.00 hours At 07.00 hours the next morning, he developed severe diarrhoea and severe abdominal pain As instructed, he sieved his loose stools and recovered four stones, each measuring 2·5 × 1·25 cm, plus about 20 pea-sized stones. He then took a herbal cure to 'reduce gallbladder inflammation' for 2 weeks He remained well for 2 years but then developed recurrent biliary colic and preferred not to repeat the herbal treatment A surgical appointment was successfully obtained, and ultrasonography showed a single large gallstone An uneventful cholecystectomy was performed and the solitary stone was retrieved Operative cholangiography showed a normal-sized bile duct with no filling defects and free flow into the duodenum Discussion with the herbalist revealed that the treatment prescribed was common in his practice and that he was not aware of any serious side-effects or sequelae. He was also not aware of any case of recurrent gallstones.

### Discussion

This case shows clear ultrasonographic evidence of a reduction in the number of gallstones following the ingestion of olive oil and lemon juice. The herbal cure is described in the literature, albeit not in the usual reading of the medical practitioner[1]. A similar case has been reported from Singapore[2]. Surprisingly, we could find no reports documenting the theoretical risk of obstructive jaundice, cholangitis and acute pancreatitis in association with the migration of gallstones through the common bile duct despite the apparent widespread use of this herbal cure. Thus, olive oil and lemon juice may be considered as an adjunct to gallstone lithotripsy or to shorten the course of treatment with oral dissolution agents.

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# Primary leiomyosarcoma of the breast

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*Correspondence to:* Mr T. W. J. Lennard

## Case report

A 58-year-old woman presented with a painless enlarging lump in the left breast. She was 11 years postmenopause and had had three children. There was no family history of breast or other disease.

She had a rounded 3 cm well circumscribed mass in the upper outer quadrant of the left breast. The lesion was not tethered deeply and there was no clinical skin or nipple involvement. The right breast was normal.

Fine needle aspiration cytology was performed and the lesion graded as AC4, suspicious of malignancy[1]. The possibility of a sarcoma was raised. Mammography (*Figure 1*) demonstrated a 4·5 cm dense lobulated and suspicious lesion in the upper outer quadrant of the left breast.

The patient underwent wide local excision with level 2 axillary lymph node sampling to achieve diagnosis and definitive therapy. The mass was well circumscribed and measured 40 mm in diameter. Histologically, the tumour had an expanding margin and excision was complete. The tumour was composed largely of anastomosing bundles of spindle-shaped cells with abundant faintly eosinophilic cytoplasm and elongated blunt-ended cigar-shaped nuclei (*Figure 2*). Occasional small clear vesicles were present in the nuclei. Small areas of the tumour had a more rounded cell appearance. There was some nuclear pleomorphism, and occasional bizarre multinucleate giant cells were present, with numerous mitotic figures (approximately ten per ten high-power fields). Small areas of pyknosis, necrosis and focal lymphocytic infiltration were seen. Some stromal hyalinization was identified. There was no evidence of any large vein from which the tumour might have arisen. Immunohistochemical staining showed the tumour to be negative for low molecular weight cytokeratins and S100 (respectively indicating that epithelial and neural origin were unlikely), weakly positive for the non-specific intermediate filament vimentin, and moderately positive for the relatively smooth muscle specific intermediate filament desmin. Immunohistochemical staining for smooth muscle actin showed moderate positivity and strong staining in a small proportion of cells. The diagnosis of primary leiomyosarcoma was made. Lymph nodes showed mild reactive changes only.

Chest radiography, and isotope bone and liver scans were normal, as were liver ultrasonography and computed tomography of the chest and liver. Subsequent management options included completion mastectomy, radiotherapy, chemotherapy and hormone therapy. Because of the complete excision of the tumour and the lack of evidence of disseminated disease, the decision was made to reserve further treatment. The patient remains well at 1 year with no clinical or mammographic evidence of recurrence.

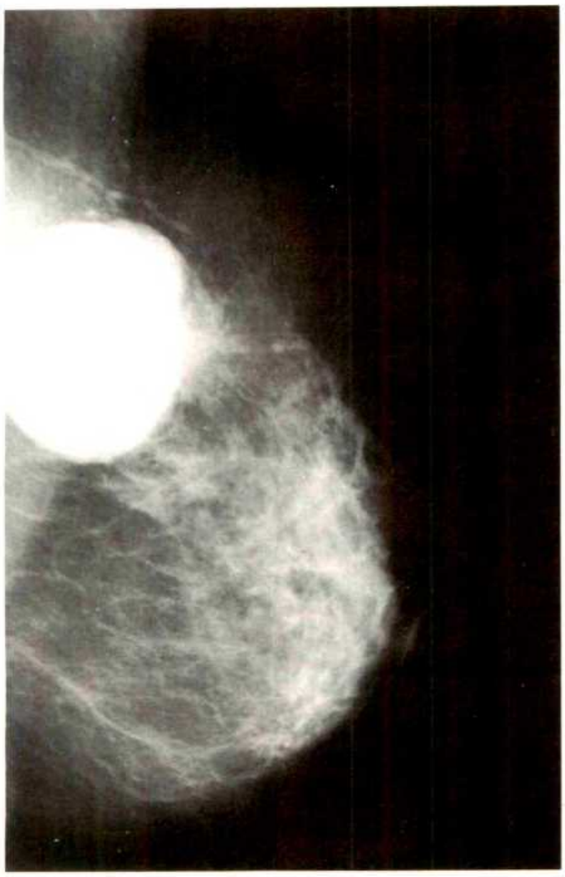

**Figure 1** *Mammogram showing the dense, well circumscribed radiographic appearance of the tumour*

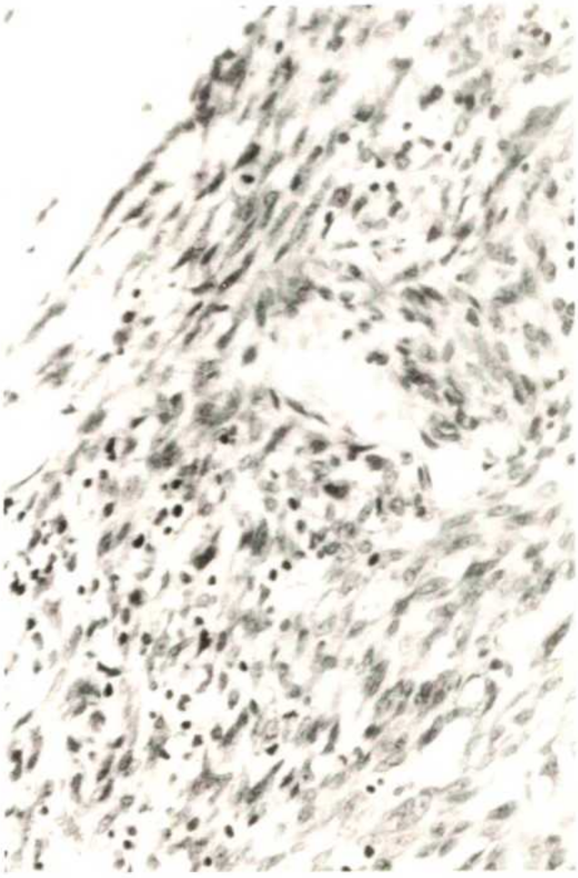

**Figure 2** *Photomicrograph of the edge of the tumour showing spindle cell morphology and several mitotic figures (haematoxylin and eosin stain, original magnification × 250)*

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**Table 1** *Clinicopathological features of reported cases of leiomyosarcoma of the breast*

| Reference | Age | Sex | Size (cm) | Circum-scription | Mitosis | Treatment | Follow-up | Tumour present? |
|---|---|---|---|---|---|---|---|---|
| Crocker and Murad[3] | 51 | M | 5 | No | Common | Radical mastectomy | None | ? |
| Haagensen[4] | 77 | F | 8 | Yes | Very frequent | Mastectomy | Alive at 14 years | No |
| Pardo-Mindán *et al.*[5] | 49 | F | 7 | Yes | 16 per 10 HPF | Simple mastectomy | Alive at 6 months | No |
| Barnes and Pietruszka[6] | 55 | F | 3 | Yes | 10 per 10 HPF | Simple mastectomy | Died at 4 years 4 months | No |
| Hernandez[7] | 53 | M | 4 | Yes | 15 per 10 HPF | Patey mastectomy | Alive at 1 year 2 months | No |
| Chen *et al.*[8] | 59 | F | 5·6 | Yes | 3 per 10 HPF | Simple mastectomy | Alive at 16 years | Yes, liver |
| Gobardhan[9] | 50 | F | 9 | No | 5 per 10 HPF | Patey mastectomy | Alive at 2 years | No |
| Yatsuka *et al.*[10] | 56 | F | 1·5 | Yes | 21 per 10 HPF | Radical mastectomy | Alive at 4 years 7 months | No |
| Nielsen[11] | 24 | F | 1·5 | Yes | 2 per 10 HPF | Local excisions, simple mastectomy | Died after 20 years | Yes, widespread |
| Arista *et al.*[12] | 50 | F | 4·5 | Yes | 4 per 10 HPF | Local excision with recurrence twice | Alive at 6 years 4 months | No |
| Waterworth *et al.* | 58 | F | 4·0 | Yes | 10 per 10 HPF | Local excision | Alive at 1 year | No |

HPF, high-power fields

## Discussion

Primary leiomyosarcoma of the breast is very rare[2]. The histological appearance described here was typical of a leiomyosarcoma and this was supported by the pattern of immunohistochemical staining. There was no evidence of any vascular channel from which this tumour might have arisen, as in other reported cases.

The 11 cases reported in the literature are summarized in *Table 1*. The mean age at presentation was 53 years. In nine patients the tumour arose in women. The tumours tend to present as large masses, the mean size being 4·8 (range 1·5–9·0) cm. They are mostly well circumscribed and are rarely tethered to skin or muscle. Mammography usually shows a dense, well circumscribed mass with little evidence of local invasion. Prognosis is difficult to determine on histopathology, although local invasion and degree of cellular atypia appear to have some predictive value, while tumour size and mitotic activity correlate less well with outcome[6,13]. Recurrence tends to be local[11] or blood-borne and in none of the reported cases has the tumour metastasized to local lymph nodes. Metastatic disease may become apparent many years later; one patient developed liver secondaries 16 years after resection of the primary tumour[8].

The uncertain behaviour and rarity of this tumour mean that precise knowledge of the best form of management is not available. Breast conservation is desirable in the management of breast cancer provided that clearance and recurrence rate are not compromised. A similar approach might be taken with leiomyosarcoma, although one reported case experienced local recurrence four times before mastectomy[11]. Local recurrence may not adversely affect survival. Wide local excision should be sufficient treatment in cases that are anatomically suitable. Mastectomy as a salvage procedure or with a large central tumour would appear to be the alternative. Lymphatic dissection seems pointless in a disease not known to spread to the local lymph glands. The roles of chemotherapy and radiotherapy are less clear, but there is little evidence to suggest that either is helpful[14].

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# Delays in care of the critically injured

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*Prehospital and resuscitation periods and times to emergency surgery were studied in major trauma victims over two 12-month periods to identify factors causing delay in emergency care. Eighteen patients required emergency surgery in the first group and 13 in the second. The mean presurgery time (i.e. time from arrival in the accident and emergency department to surgery) was 117 min in the first group and 111 min in the second. Causes of delay included a sequential approach to resuscitation and investigation, limited staff and theatre availability, and failure to call the trauma team. Times for resuscitation and times to surgery could be reduced by earlier decision-making, alerting key personnel promptly and performing tasks in parallel.*

All services dealing with major trauma should audit their performance to discover those factors that contribute to the reported preventable mortality rate of 67 per cent for injuries not involving the central nervous system (CNS) and of 17 per cent for CNS-related injuries[1]. Previous audit of performance in the management of major trauma in the accident and emergency department of the Royal Victoria Hospital, Belfast highlighted many deficiencies in the management of major trauma[2]. Changes in medical staff, the introduction of the Revised Trauma Score as a triage tool, and the creation of a 'trauma team' brought a significant improvement in patient management[3]. This study measures the duration of the prehospital and presurgical phases (including time in the accident and emergency department and time *en route* to surgery) and analyses their relationship to type of injury and causes of delay.

## Patients and methods

The Royal Victoria Hospital's accident and emergency department receives 46000 new patients per year and accepts major trauma cases from a catchment area of approximately 275 square miles. A trauma team consisting of senior anaesthetic, surgical, and accident and emergency staff sees all patients with an abnormal Revised Trauma Score (triage version) in the accident and emergency department. Cardiothoracic and neurosurgical specialities are on site.

Ambulance crews had basic training at the time of the study. The ambulance system carried out a weekly audit to ensure ORCON (UK ambulance response-time requirements) standards for 999 emergency calls are met, i.e. that 95 per cent have an ambulance dispatched within 3 min, that 95 per cent of incidents are reached in less than 20 min and 20 per cent in less than 8 min.

Data on all major trauma victims with an Injury Severity Score (ISS) of more than 15 were recorded prospectively on a computer during 1987 (group A). The length of time spent in the accident and emergency department (resuscitation time) and that from leaving the department to the commencement of surgery (presurgical time) were recorded for those patients receiving emergency operations for life-threatening visceral, intracranial or vascular injury. Commencement of surgery was defined as the onset of inhalational anaesthesia in theatre or the time of arrival in the operating room when anaesthesia was commenced in the accident and emergency department. In the year commencing 1 August 1989, the causes of delay in these phases, if any, were investigated (group B). Prehospital times were obtained from ambulance control, where all 999 calls were taped and recorded, and included activation, response, scene, transport and arrival times.

## Results

### *Group A*

Fifty-four patients were included; 35 had blunt injuries, one had been stabbed and 18 had gunshot wounds. The mean ISS was 30 (median 25, range 16–75). Eighteen patients required emergency surgery. No patient was trapped at the scene. Six patients were brought in dead and were excluded from the study. Six died in the accident and emergency department and a further 20 of the 54 patients eventually died as a consequence of trauma. Mean prehospital times were 15 min for the whole group and 13 min for those requiring emergency surgery.

Resuscitation time, including radiography, was a mean of 58 min. The mean presurgical time, including computed tomography and time spent waiting for theatre outside the accident and emergency department, was 59 min. Times are shown in *Table 1*. Resuscitation times ranged from 15 to 120 min and presurgical times ranged from 21 to 305 min. Eight patients arrived between 24.00 and 08.00 hours, six between 08.00 and 16.00 hours, and four between 16.00 and 24.00 hours.

### *Group B*

There were 13 patients in group B, six with penetrating and seven with blunt injuries. Two patients died. Only two patients were hypotensive on arrival. Mean resuscitation time from arrival to surgery was 111 min, and 93 min from the time of the decision that emergency surgery was required (excluding one case of delayed diagnosis taking 12·5 h). Times are shown in *Table 1*.

In some of these cases delay in the accident and emergency department was due partly to awaiting theatre space. Only one of these patients arrived between 08.00 and 16.00 hours, five arrived in the evening, and seven between 24.00 and 08.00 hours.

### *Causes of delay (group B only)*

*Resuscitation.* All cases were approached in a sequential fashion, i.e. procedures such as intubation, chest drain insertion, catheterization, peritoneal lavage and radiography were performed consecutively rather than simultaneously.

Junior staff required senior assistance before performing a procedure (peritoneal lavage, one case; intubating head injuries, two cases).

Non-critical radiography was performed in four cases, e.g. peripheral limb radiography when intra-abdominal haemorrhage had been proven. In all cases a portable radiography machine was requested after the patient had arrived.

One patient arrived on a non-receiving day when a skeleton staff was present.

The trauma team was not called for one patient who fitted the triage criteria. Peritoneal lavage 12 h later was positive and a lacerated lobe of liver was sutured.

*Presurgical causes.* Lack of theatre space or anaesthetic personnel occurred in five cases. (This is relative, as these five

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**Table 1** *Times taken to emergency surgery*

| | No. of patients for surgery | Mean presurgical time (min) | | |
|---|---|---|---|---|
| | | Accident and emergency department | Elsewhere | Total |
| Group A* | | | | |
| Hypotensive due to blood loss† | | | | |
| Blunt | 5 | 77 | 122 | 199 |
| Penetrating | 5 | 31 | 60 | 91 |
| Normotensive | | | | |
| Blunt | 2 | 58 | 27 | 85 |
| Penetrating | 6 | 62 | 27 | 99 |
| Total | 18 | 58 | 59 | 117 |
| Group B | | | | |
| Blunt | 7 | 90 | 49 | 139 |
| Penetrating | 6 | 52 | 31 | 83 |
| Total* | 13 | 63 | 48 | 111 |

*One patient with delayed diagnosis excluded; †on arrival in the accident and emergency department

**Table 2** *Mean prehospital times found in several studies*

| Reference | Site | Time (min) | | | | Paramedics | Area (square miles) |
|---|---|---|---|---|---|---|---|
| | | Response | Scene | Transport | Total | | |
| 4 | Houston | 5·32 | 15·8 | 11·7 | 32·6 | Yes | 700 |
| 5 | Washington | 12·3 | 24·9 | 19·4 | 56·6 | Yes | 714 |
| 6 | Orange County, California (median) | — | — | 8·0 | 23·0 | Yes | 784 |
| 7 | Denver | 4·66 | 9·79 | 6·04 | 20·49 | Yes | — |
| 8 | Ohio | 4·6 | — | — | 29·0 | Yes | — |
| | Belfast | 4·57 | 4·96 | 4·83 | 14·36 | No | 275 |

patients had been stabilized with moderate amounts of fluid. Had their condition been more critical, surgical haemostasis might have been obtained more rapidly.)

Computed tomography: three patients took an average of 30 min each undergoing this procedure. One patient with a penetrating injury had to wait for the scanner to be prepared.

In one case consultant opinion was required before surgery could commence.

In one case staff and equipment had to be mobilized for cardiopulmonary bypass.

## Discussion

Prehospital times in this study compare favourably with results from other urban trauma centres (*Table 2*). None of the patients brought in dead was trapped at the scene. The scene times for ambulance workers in other studies are longer than in this study (*Table 2*) and may be related to a different approach by ambulance workers or entrapment. Prehospital care was rapid, but 19 patients required emergency intubation in the accident and emergency department and might have benefited from on-scene intubation as some authors have suggested[9,10]. The advantages of prehospital intravenous therapy have not been clearly established[9–13]. Some studies show benefits[14–16] but others believe that 'scoop and run' may be the best policy[17].

Faster resuscitation is possible: for example, for 79 patients in Portland, Oregon, USA with an ISS greater than 15, mean times of 34 min were reported[18]. In addition, transfers to surgery can be accomplished in less than 9 min[17]. Studies of preventable trauma deaths have shown that delayed surgery is one of the major contributing factors[1,19,20]. Others have recommended resuscitation in theatre[21].

For rapid and efficient resuscitation a sequential approach should not be taken. After the primary survey, depending on the staff available, patient assessment and priority, procedures should be performed simultaneously, e.g. insertion of intravenous lines, chest drains and diagnostic peritoneal lavage can be performed together. If staff wear lead aprons, work need not stop for portable radiography.

Delays occur when junior staff are unable to act or senior anaesthetic and surgical personnel are not available to go to the accident and emergency department. The senior accident and emergency department member of the trauma team must be able to perform all the practical procedures the patient requires and make the decision for further investigations, e.g. computed tomography or definitive surgery.

Non-critical radiographic scans should be taken in theatre if they cannot be performed in parallel, and should not delay transfer to surgery. A portable radiography machine and radiographer, and plates for lateral cervical spine and chest radiographs, should be requested after the standby call and be ready when the patient arrives. Orthopaedic surgeons should be called early and radiographs taken before the patient is ready for theatre.

New or inexperienced staff are more likely to forget to call the trauma team. Senior nurses are more familiar with the criteria for calling the trauma team (*Table 3*) and are more likely to remember to do so.

Presurgical delays include lack of theatre space and staff, which affects all surgical specialities; the trauma patient may not be first priority. Putting theatre on standby when the ambulance standby call is received prevents commencement of less urgent cases.

For computed tomography and cardiac bypass, locating and alerting neurosurgeons, radiographers and technicians can begin with the standby call in some instances. Staff should be called as soon as the decision to scan is made.

The need for a senior opinion will always be a problem when senior medical staff are not on site. Delay can be reduced if

**Table 3** *Triage version of Revised Trauma Score*

| | |
|---|---|
| Abnormal physiology | Glasgow Coma Scale <12/14<br>Systolic blood pressure <90 mmHg<br>Respiratory rate >30 or <10 |
| Obvious serious injury | Penetrating injury to chest, abdomen, head, neck, groin<br>Two or more proximal long bone fractures<br>Burns >15 per cent, or to face or airway<br>Flail chest |
| Evidence of high-energy impact | Fall of 6 m or more<br>High-speed crash<br>Ejection of patient<br>Death of same car occupant<br>Pedestrian hit at speed (>20 miles per hour)<br>Backward displacement of front axle<br>Compartment intrusion 38 cm (15 inches) or more on patient's side |

Adapted from Reference 22

this need is anticipated by ambulance workers using the Revised Trauma Score triage version, and the hospital is warned.

This study is too small to show any significant future impact by prospective analysis. By reducing the time interval between arrival in the accident and emergency department and definitive surgery, mortality and morbidity rates should be reduced. Shorter times to surgery would be expected to reduce multiorgan failure, sepsis, brain damage and transfusion-related problems.

A practised, efficient and rapid system would improve prognosis in those cases where time is most critical: massive blood loss or major cardiac injury and both minor and major disasters.

Because staff availability for the care of trauma patients in the UK varies, it is not possible to have predetermined roles as occurs in trauma centres in other countries. The above proposals should reduce delay by commencing the most time-consuming, important interventions early and simultaneously.

The report of the working party of the Royal College of Surgeons of England in 1988 on the management of patients with major injuries[23] recommended the creation of trauma centres and advanced training of ambulance workers. Until then, it is important to optimize the services that are available.

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# Massive lower gastrointestinal haemorrhage from a splenic artery pseudoaneurysm

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Visceral arterial aneurysms and pseudoaneurysms leaking into the colon are rare. Most reported cases have occurred after chronic pancreatitis.

We report a rare case of massive lower gastrointestinal haemorrhage due to a pseudoaneurysm of the splenic artery which had eroded into the colon. The patient had no evidence of pancreatitis and no other known predisposing causes.

## Case report

A 40-year-old Chinese man was admitted on 3 March 1991 with a 2-day history of frequent passage of small amounts of fresh blood from the rectum. There was no other relevant history except that he had undergone a Pólya partial gastrectomy 7 years earlier for a gastric ulcer. He was not on any ulcerogenic drugs and did not abuse alcohol. On examination, he looked well but had severe pallor. There was no abnormality on abdominal or rectal examination. He was transfused as his haemoglobin level was only 3·1 g/dl. At gastroscopy, no bleeding source was detected in the stomach or remnant duodenum, and a sigmoidoscopic examination up to 25 cm was also normal.

The patient rebled 7 h after admission. An urgent selective visceral angiogram revealed a saccular lobulated aneurysm arising from the splenic artery (*Figure 1*). However, no focal bleeding point or extravasation of the contrast was identified in the stomach or intestine. A technetium-99$^m$ pertechnetate scan of the abdomen also showed no evidence of a bleeding source. About 30 h after admission, he became hypotensive following a massive bleed. An attempt at colonoscopy was abandoned as the view was obscured by fresh bleeding. He was prepared for operation.

At operation a large mass was found in the left side of the abdomen involving the spleen, tail of the pancreas, remnant stomach, left kidney and mesocolon. This was initially thought to be a large retroperitoneal tumour, but no tumour spread was noted elsewhere in the peritoneum. During the dissection to separate the spleen and the stomach remnant, a cavity containing a large amount of clot was entered. Further dissection after removal of the clot revealed a 1 cm diameter opening into the splenic flexure of the colon which was otherwise normal. The pancreas and other organs were all normal. Splenectomy was performed with ligation of the splenic artery and segmental resection of the colon, followed by end-to-end anastomosis. The patient made an uneventful postoperative recovery.

## Discussion

It is rare for visceral artery aneurysms to bleed directly into the colon. Most cases of bleeding occur intraperitoneally, into the upper gastrointestinal tract or into a pancreatic pseudocyst. Colonic bleeding occurs commonly after erosion of a pancreatic pseudocyst or abscess into the colon rather than directly from an aneurysm[1]. In this patient, the remote possibility of the splenic artery aneurysm bleeding into the colon was not entertained as no leakage of dye into the intestine was seen on the angiograms.

When a pseudoaneurysm becomes adherent to the adjacent organs, it can be mistaken for a malignant tumour. Indeed, in this case, the initial diagnosis was an advanced tumour until after the pseudoaneurysm was entered during mobilization of the mass. In a previous report of a case associated with chronic pancreatitis, the intraoperative findings were mistaken for carcinomatosis peritonei; the splenic artery pseudoaneurysm was diagnosed only after operation by computed tomography and angiography[2].

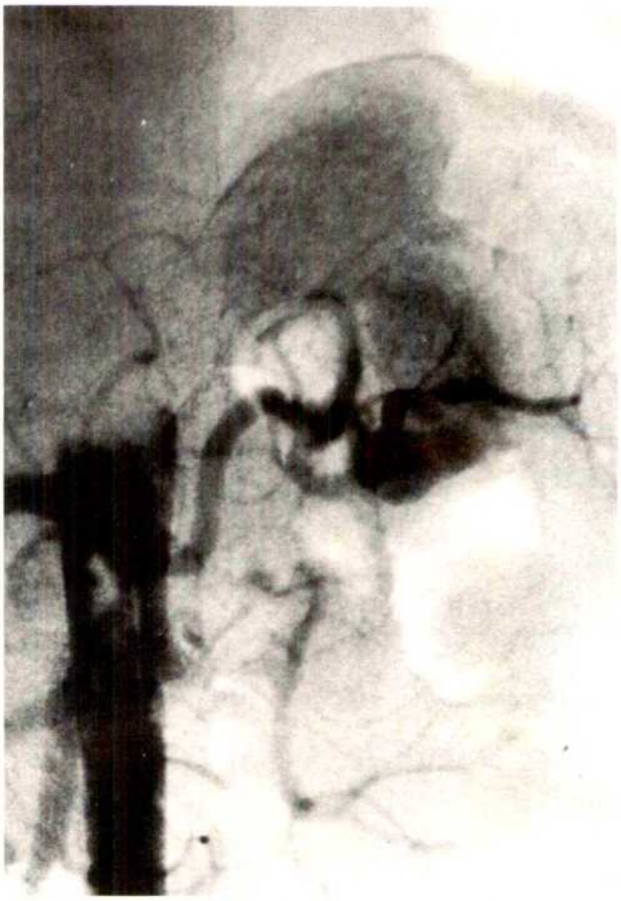

**Figure 1** *Angiogram showing the splenic artery aneurysm*

If diagnosed before operation, pseudoaneurysms can be treated by embolization of the splenic artery[3–5]. Even in patients with a colonic fistula, the healing of the colonic mucosa has been achieved after embolization of the splenic artery pseudoaneurysm[2].

Most visceral artery pseudoaneurysms are caused by pancreatitis, biopsies or operative trauma[6]. The aetiology of the pseudoaneurysm in this patient remains uncertain, although trauma to the splenic artery during the earlier gastrectomy is a possible cause. If so, it is interesting that this patient had no previous symptoms and that the pseudoaneurysm took 7 years to erode into the colon.

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# Age-standardized incidence of ruptured aortic aneurysm in a defined Swedish population between 1952 and 1988: mortality rate and operative results

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*The incidence and mortality rate of ruptured aortic aneurysm in a defined and stable Swedish population was determined for the period 1952–1988. The annual rupture rate of abdominal aneurysm rose significantly from 0·9 per 100 000 inhabitants in the 1950s to 6·9 in the 1980s. After standardization for age, the mortality rate increased between 1960 and 1988 by 2·4 per cent annually (95 per cent confidence interval 1·2–3·6 per cent,* $P = 0\cdot0004$*). Comparable figures from the UK during the 1980s have been reported to be two to three times higher. The mortality rate of ruptured thoracic aneurysm in the Swedish population did not increase when adjusted for age. In the 1980s the overall mortality rate of ruptured abdominal aneurysm was 85 per cent. Death occurred outside surgical clinics in 52 per cent of cases; 37 per cent of the total number of patients with ruptured aneurysm reached the operating table but only 30 per cent underwent aortic reconstruction. Patients treated by vascular surgeons had lower blood loss and transfusion needs, shorter aortic clamp time and operation time, and lower mortality rate than patients treated by non-specialized general surgeons. Specialized vascular surgeons also completed the reconstruction, and used straight grafts, in a higher proportion of cases than general surgeons.*

It may be questioned whether an increasing number of patients presenting with ruptured abdominal aortic aneurysms[1,2] represents a true increment of incidence or a better awareness of the disease and improved diagnostic tools leading to an increase in referral to hospital. The answer to this question requires accurate knowledge of deaths occurring outside hospital. Population-based studies have indicated a true increase of incidence in the UK[3–5] and Australia[6] during the past 20 years. However, a comparable study in Sweden[7], encompassing a single year, showed a considerably lower incidence of ruptured abdominal aortic aneurysm. The true overall incidence in Sweden is not known, and the difference in population incidence compared with the UK based on an assessment of 1 year is uncertain. In addition, the increased incidence found in the UK and Australia might to some extent reflect the ageing of the population since age is one of the strongest risk factors for arteriosclerosis.

The objectives of this study were to determine whether the incidence of ruptured abdominal aortic aneurysm in a Swedish population has increased, and to evaluate whether the technical developments in anaesthesia and surgery of recent years have significantly reduced the overall mortality rate of ruptured aortic aneurysm in Sweden.

## Patients and methods

The evaluated population consisted of residents in the city of Göteborg; during the 37-year study period (1952–1988) the number of inhabitants rose steadily from 363 000 to 431 000 and the population was otherwise stable with little migration.

To find all patients who had died from rupture of the aorta all operation calendars of the surgical clinics were reviewed. The diagnoses at discharge from hospital were studied in both operating and non-operating specialties. All autopsy reports, from the department of clinical pathology and from the department of forensic medicine, were reviewed. Details of patients with a death certificate code (International Classification of Diseases) indicating aneurysmal disease were retrieved from the Swedish Central Statistical Bureau. Residents from outside the city who died when visiting Göteborg were excluded. Death certificates for residents from the city who died elsewhere were sent to the city authorities. Thus, these certificates were available for evaluation and additional information could be retrieved when needed. During the study period Swedish law made it compulsory to perform autopsy at the department of forensic medicine on patients dying outside hospital, and so death outside hospital was subject to autopsy in nearly 100 per cent of cases. Death from aneurysm rupture in connection with surgery was included, by definition, in the immediate 30-day postoperative mortality statistics. Late fatal sequelae after aneurysm repair such as graft-enteric fistula and erosion were not regarded as death from aneurysm rupture (eight cases during the study period). Patients with ruptured aneurysm of the major branches of the aorta were excluded (20 cases during the study period).

The site of rupture determined the classification of the aneurysm regardless of the extent of the aneurysmal dilatation. Thus, a rupture above the diaphragm of a thoracoabdominal aneurysm was regarded as a ruptured thoracic aneurysm (16 cases) and the only case of rupture of such an aneurysm below the diaphragm was regarded as abdominal aneurysm rupture.

In Sweden vascular surgery is not a formal surgical specialty separate from general surgery. However, since the early 1970s an informal subspecialization has emerged, which has made it possible to compare the surgical results of 'vascular surgeons' performing regular elective vascular surgery with those of 'general surgeons' performing only occasional emergency vascular procedures during the last 10 years of the study.

The age distribution of the population in 1970 was used in calculations of age standardization[8]. Data for age standardization were available only after 1960. Statistical computations of changes in incidence over time were performed by analysis of variance. Comparison of means was performed by Student's $t$ test and proportions by $\chi^2$ test. Figures are given as mean(s.e.m.) unless otherwise stated. Two-tailed tests were used and $P < 0\cdot05$ was considered significant.

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## Results

### *Abdominal aortic aneurysm*

Aneurysm rupture occurred in 611 patients, of whom 454 (74 per cent) were men and 157 (26 per cent) were women ($P < 0{\cdot}01$). The mean age at rupture was 75·1(0·4) years, range 44–96 years, and the median age 74 years for both sexes. The age at rupture showed a statistical trend to increase during the study period ($P = 0{\cdot}064$). The overall mortality rate (within 30 days of rupture) was 89 per cent. Fifty per cent of the patients died in hospital at a surgical clinic, 14 per cent at non-surgical clinics, 10 per cent in nursing homes and 26 per cent outside hospital. The diagnosis has been confirmed by operation and/or clinical autopsy in 72 per cent and by autopsy at the department of forensic medicine in 26 per cent. Thus, only 2 per cent of the ruptured aneurysms were diagnosed on clinical grounds alone. *Table 1* shows the information presented for various decades. The incidence of ruptured aortic aneurysm during the study period increased significantly (*Figure 1*) ($P < 0{\cdot}0001$). The proportion of patients undergoing operation with aortic reconstruction has increased, as has the use of straight vascular prostheses compared with bifurcation prostheses (*Table 1, Figure 2*).

Annual mortality rate for ruptured abdominal aortic aneurysm when standardized for age is shown in *Figure 3*. The incidence increased during the period 1960–1988 by 2·4 per cent per year (95 per cent confidence interval 1·2–3·6 per cent; $P = 0{\cdot}0004$). *Figure 4* shows the increasing numbers of operations for both ruptured and non-ruptured abdominal aortic aneurysm. Between 1980 and 1988 the mean(s.e.m.)

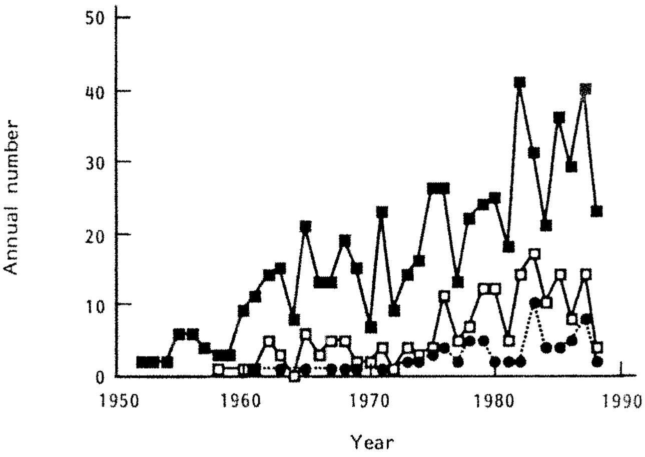

**Figure 2** *Incidence of ruptured abdominal aortic aneurysm (■), operations for rupture (□) and survivors after acute repair of rupture (●)*

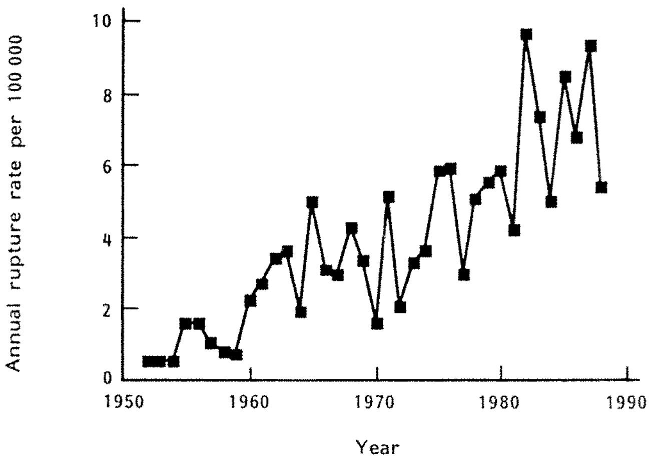

**Figure 1** *Annual incidence of rupture of abdominal aortic aneurysm per 100 000 population of Göteborg over the period 1952–1988. The incidence increased significantly* (P < 0·0001)

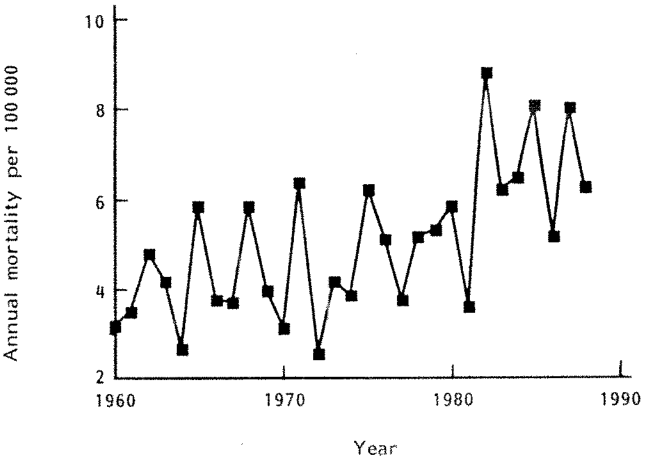

**Figure 3** *Age-standardized mortality rate for ruptured abdominal aortic aneurysm in Göteborg from 1960 to 1988. The annual mortality rate increased by 2·4 per cent per year (95 per cent confidence interval 1·2–3·6 per cent,* P = *0·0004)*

**Table 1** *Ruptured abdominal aortic aneurysm in the Göteborg population over the period 1952–1988*

| | 1952–1959 | 1960–1969 | 1970–1979 | 1980–1988 |
|---|---|---|---|---|
| Number of cases | 28 | 138 | 180 | 264 |
| Sex ratio (M:F) | 22:6 | 93:45 | 134:46 | 204:60 |
| Mean(s.e.m.) age (years) | 72·5(1·8) | 74·2(0·8) | 75·7(0·7) | 75·3(0·5) |
| Proportion operated on (%) | 3·6 | 22 | 30 | 37 |
| Mean(s.e.m.) age at operation (years) | 69·3(1·3) | 71·4(1·1) | 71·0(0·7) | 71·1(0·8) |
| Proportion reconstructed (%) | 3·6 | 13 | 24 | 30 |
| Operation (*n*) | | | | |
| Bifurcation graft | 1 | 16 | 43 | 56 |
| Straight graft | 0 | 2 | 0 | 23 |
| Exploration alone | 0 | 13 | 11 | 19 |
| Place of death (%) | | | | |
| Surgical clinic | 43 | 60 | 46 | 48 |
| Non-surgical clinic | 18 | 12 | 16 | 12 |
| Geriatric care | 25 | 11 | 8 | 9 |
| Outside hospital | 14 | 17 | 30 | 31 |
| 30-Day mortality rate (%) | | | | |
| Overall | 100 | 96 | 87 | 85 |
| Reconstructed cases | 100 | 72 | 44 | 50 |

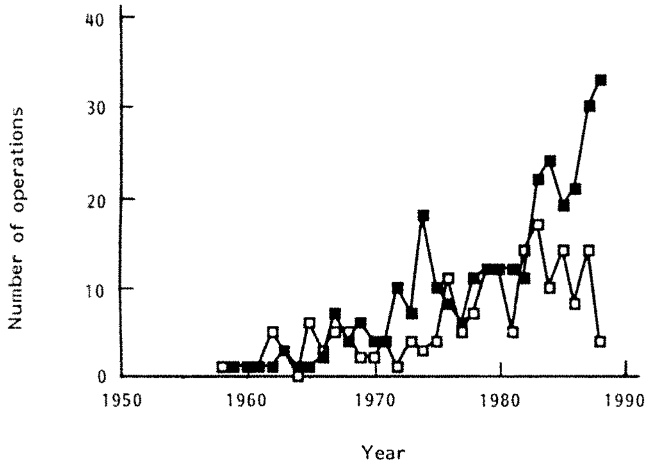

**Figure 4** *Number of operations for ruptured (□) and non-ruptured (■) abdominal aortic aneurysm in Göteborg between 1952 and 1988. No operations were performed before 1958*

**Table 2** *Results of operation for ruptured abdominal aortic aneurysm in the period 1979–1988, by either vascular or general surgeons**

| | 'Vascular' surgeon | 'General' surgeon | *P* |
|---|---|---|---|
| Number of operations | 69 | 63 | |
| Age at operation (years) | 69·8(0·9) | 72·5(0·8) | 0·02 |
| Year of operation (median) | 1983·8 | 1983·0 | n.s. |
| Admission systolic blood pressure (mmHg) | 102(5) | 101(6) | n.s. |
| Admission diastolic blood pressure (mmHg) | 82(3) | 83(4) | n.s. |
| Admission pulse rate (beats/min) | 95(3) | 98(4) | n.s. |
| Period of preoperative shock (systolic blood pressure <80 mmHg) (%) | 73 | 82 | n.s. |
| Preoperative haemoglobin concentration (g/l) | 118(3) | 122(3) | n.s. |
| Preoperative creatinine concentration (μmol/l) | 159(13) | 141(10) | n.s. |
| Operation | | | |
| Bifurcation graft | 42 | 41 | |
| Straight graft | 21 | 5 | 0·0015 |
| Exploration alone | 6 | 17 | |
| Operation time (min) | 236(10) | 343(19) | 0·001 |
| Peroperative blood loss (ml) | 5756(571) | 7719(881) | 0·05 |
| Aorta clamp time (min) | 99(6) | 158(12) | 0·0001 |
| Blood transfusion during the per- and post-operative periods (ml) | 6898(666) | 10930(1015) | 0·008 |
| Maximum postoperative creatinine concentration (μmol/l) | 402(45) | 452(54) | n.s. |
| Postoperative time on ventilator (h) | 183(31) | 207(34) | n.s. |
| Postoperative intensive care (days) | 11·5(1·4) | 13·7(3·2) | n.s. |
| Postoperative wound infection (*n*) | 0 | 2 | |
| 30-Day mortality rate (%) | 48 | 76 | 0·0008 |
| Hospital stay (days) | 20·0(2·3) | 24·3(4·3) | n.s. |
| Late graft infection (*n*) | 0 | 1 | |

*Only patients who had completed reconstruction of the aorta were included in the calculations of operation time, peroperative blood loss, aortic clamp time, blood transfusion, maximal postoperative creatinine concentration in serum, and postoperative hospital stay. Unless otherwise stated values are mean(s.e.m.). n.s., Not significant

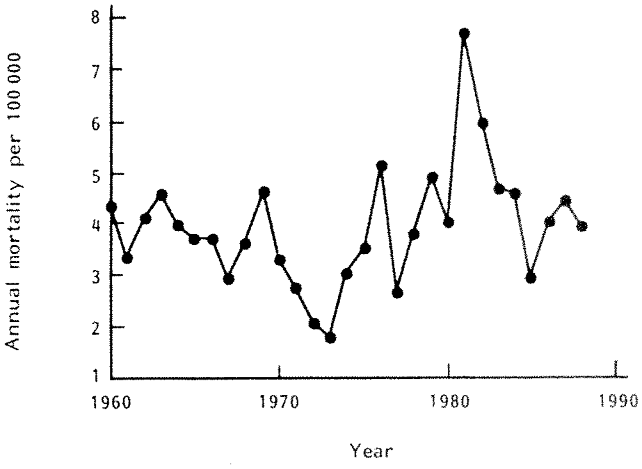

**Figure 5** *Age-standardized mortality rate from ruptured thoracic aortic aneurysm in Göteborg between 1960 and 1988. The incidence did not change significantly* (P = *0·26*)

number of operations (frequency) for ruptured aneurysm was 2·6(0·35) per 100000 inhabitants and 4·2(0·52) per 100000 inhabitants for non-ruptured aneurysms. The mean age at operation in patients with ruptured aneurysms is shown in *Table 1*. Patients operated on for non-ruptured aneurysms were significantly younger than those with ruptured aneurysms. Mean(s.e.m.) age at operation for non-ruptured aneurysm was 66·5(2·0) years in the 1960s, 66·4(0·8) years in the 1970s and 68·9(0·6) years in the 1980s.

During the period 1979–1988, 69 patients with ruptured abdominal aortic aneurysm were treated by vascular surgeons and 63 by general surgeons (*Table 2*). The allocation to different surgeons was more or less random. The preoperative conditions of patients were comparable when operated on, irrespective of the type of surgeon. Vascular surgeons used straight prostheses in a higher proportion than general surgeons. Operation time, peroperative blood loss, aortic cross-clamp time, total volume of blood transfusion during hospital stay, and 30-day mortality rate were all significantly lower in the group of patients operated on by vascular surgeons.

### *Thoracic aortic aneurysm*

Aneurysm rupture and death occurred in 590 patients. The mean(s.e.m.) age at rupture was 71·2(0·5) years, range 15–97 years, and the median age was 69·8 years. The sex distribution was 54 per cent men and 46 per cent women. Patients with ruptured thoracic aneurysm had a lower age (by 4 years on average) and a different sex distribution (considerably more women) than patients with ruptured abdominal aneurysm. Of the former patients 14 per cent died in hospital at a surgical clinic, 28 per cent at non-surgical clinics, 11 per cent in nursing homes, and 47 per cent died outside hospital. The cause of death was confirmed by clinical autopsy and/or operation in 53 per cent and by forensic autopsy in 47 per cent. The site of rupture was in the ascending aorta in 65 per cent, in the aortic arch in 10 per cent and in the descending aorta in 25 per cent. None of these proportions changed significantly during the study period. The uncorrected incidence of aneurysm mortality increased significantly but this increase disappeared after age standardization (*Figure 5*, *P* = 0·26).

## Discussion

This investigation confirms a significant rise in the incidence of ruptured abdominal aortic aneurysm with ensuing mortality between 1952 and 1988 when standardized for age; no such increase was observed for thoracic aortic aneurysm. The figures for the incidence of ruptured abdominal aneurysm over the period 1980–1988 are almost identical to those described in another Swedish investigation[7]. In contrast, the corresponding

**Table 3** *Annual rupture rate of abdominal aortic aneurysm in Sweden and the UK*

| Place | Study period | Annual rupture rate per 100 000 |
|---|---|---|
| Göteborg* (Sweden) | 1952–1959 | 0·9 |
| | 1960–1969 | 3·2 |
| | 1970–1979 | 4·1 |
| | 1980–1988 | 6·9 |
| Stockholm[7] (Sweden) | 1980 | 6 |
| London[5] (UK) | 1981 | 13 |
| | 1986 | 21 |
| Worthing[4] (UK) | 1979 | 9·2 |
| | 1986 | 17·5 |
| Swansea[3] (UK) | 1974 | 7 |
| | 1980 | 10 |
| | 1983 | 17 |

*Present study

incidence during the same time period in the UK has been reported to be two or three times higher[3–5] (*Table 3*). This difference should be explained by various population factors rather than deficiencies in the collection of cases in the present study. Göteborg had a stable population with no referrals to hospitals outside the city and a high proportion of autopsies were performed. To reach a high validity of establishing cause of death requires study of original information in hospital records, operation charts and autopsy protocols, since registers indicating cause of death have been found to be inaccurate[9]. Results may also vary over time due to changing codification in the International Classification of Diseases. Therefore, in the present study, we reviewed all original information sources and so achieved reliable data. A few hospital inpatients might still have been overlooked, for instance patients with a concomitant severe disease such as terminal malignancy or heart disease in whom a death certificate might have been issued without autopsy, but it was estimated that this proportion was less than 10 per cent.

The reason for the higher frequency of ruptured abdominal aortic aneurysm in the UK population is not certain. Differences in age distribution, dietary and smoking habits, and genetic disposition are possible factors. A rise over time in the incidence of abdominal aortic rupture was seen in the present study and in reports from both the UK[3–5] and Australia[6], although various investigators have reported different incidences. Such an increase may, however, reflect a higher proportion of elderly in the population unless this factor is controlled. The importance of age adjustment is apparent from the incidence of ruptured thoracic aneurysm in the present report, since a significant incidence disappeared when adjusted for age.

The reasons for a difference in mortality rate between thoracic and abdominal aneurysms in the present investigation are unclear. A possible explanation might be that non-arteriosclerotic thoracic aneurysms constitute a significant part of thoracic aortic ruptures. Degenerative lesions in the media of the vessel are a common cause of rupture in the thoracic part, but not in the abdominal part, of the aorta[10]. Whether the incidence of ruptured *arteriosclerotic* thoracic aneurysm would show an increase similar to that found for abdominal aneurysm is not known; surgical protocols and autopsy reports contained information on aneurysm configuration and site of rupture, but detailed information on size and distinction between arteriosclerotic and dissecting aneurysms was generally inadequate.

The overall mortality rate from ruptured abdominal aneurysm in this study was 85 per cent between 1980 and 1988, which is comparable to previously described figures of 80–94 per cent[3,5,7]. About half of patients who died from ruptured abdominal aneurysm were admitted to a surgical clinic at the time of death and so had at least the possibility of being considered for surgical treatment. Between 10 and 20 per cent of the patients died when they were admitted to clinics other than surgical; this emphasizes the need for clinicians to be aware of the symptoms of an expanding aneurysm. During the last two decades around 40 per cent of deaths attributable to abdominal aneurysm rupture occurred at home; previous investigations have reported proportions between 27 and 64 per cent of total mortality at home[3,5,7]. Between 1980 and 1988, 37 per cent of patients with ruptured abdominal aortic aneurysm were operated on; 7 per cent were, however, in such bad condition that they did not survive long enough to undergo a complete surgical reconstruction. Of those who survived the operation, 50 per cent survived beyond 30 days, similar to the rates of 37–62 per cent reported by others[3,5,7,11].

The present data show that the outcome of surgery was significantly better when surgeons who specialized in vascular surgery carried out the operation; similar results have been reported by others[12]. The mortality rate following elective repair of abdominal aneurysm is as low as 1·9–4 per cent[6,13]. Elective operation is therefore the most effective means of reducing mortality from aneurysm rupture. However, the opportunity to improve results requires a correct diagnosis before rupture has occurred; a greater awareness of aneurysmal disease among doctors and patients might bring earlier diagnosis. Because one-third of aneurysms may still be overlooked on clinical examination alone[14], ultrasonography has been advocated for screening purposes[15–17].

As ageing of the population did not explain the increased incidence and mortality rate of abdominal aneurysm, lifestyle-related factors, such as dietary and smoking habits, might play a role. The age at rupture showed a statistical trend to increase significantly during the study period. Furthermore, the proportion of patients requiring assistance in their daily activities of living has not increased over time. These factors contradict a possible view that the rise in mortality rate from ruptured aneurysm is just a natural consequence of an ageing population. So far, elective operation is the best means of avoiding rupture and this is feasible with a mortality rate of between 4·7 and 8·6 per cent, even in octogenarians[18,19].

In summary, the age-standardized incidence of abdominal aortic aneurysm rupture has increased in a Swedish population. The overall mortality rate from ruptured aneurysm has continued to be around 85 per cent despite a remarkable technical development in surgical procedure, anaesthesia and intensive care. This discouraging observation was explained by the fact that two-thirds of patients died before they reached an appropriate hospital and those who underwent operation were not treated by vascular surgical specialists to any significant extent. Operation performed by vascular surgeons significantly improved the outcome of ruptured aneurysm. This knowledge must be considered in the planning and organization of surgical care. Whether an increasing frequency of elective aneurysm operations will reduce the overall population mortality rate can only be answered by a prospective population study.

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# Correspondence

## Statistical aspects of research methodology

*Sir*

I read the recent article by Dr Murray (*Br J Surg* 1991; **78**: 777–81) with great interest but am left with some uncertainty as far as randomization is concerned.

We are often told that to randomize by odd and even hospital number is not strictly correct. But hospital numbers are randomly allocated on a 'first come first served' basis, and it is also entirely random whether patients with the disease process of interest acquire odd or even numbers.

Take as a contrast randomization in blocks, much used by statisticians in large national studies. This is where equal numbers in the groups of interest are distributed between centres to overcome problems from surgeon-related variability or the differences in levels of skill between different centres. Let $N$ be the number of patients in each block and let us consider the comparison of three drugs or surgical procedures, A, B, and C.

For simplicity, suppose $N = 6$, although of course it is usual for blocks to be somewhat larger than this. Then there is an equal chance that the first draw will be A, B, or C; but the second and subsequent draws will not be random. If A is drawn first, then at the second draw the probability of drawing the other A will be one in five compared with two in five for either B or C. By the last draw the outcome is completely determined. It can be seen that, far from the possible subtle and, in my view, unbelievable, rationalizations brought to bear against randomization by hospital number, randomization as recommended by statisticians is far from random!

Let us even consider the more usual but now less widely used method of employing random numbers to assign decisions on sealed cards. After making a choice by opening the card the only way of strictly maintaining the randomization is to reseal the card and re-enter it into the general pool. In my experience this is never done; the used card is discarded. But this has effects similar to the ones described above on later randomizations: if A is chosen then the subsequent freedom for A to be chosen is restricted by one, such restrictions not being in force for B or C. The effect can be made more obvious if, for example, A is by chance chosen four or five times in a row; the loss of freedom within the remaining cards at the next or subsequent draws is clear.

Hospital number, on the other hand, is so simple to use that compelling statistical arguments should be available before we should accept that its use is unacceptable.

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### Author's reply

*Sir*

As Mr Phillips remarks, there are indeed several subtle, technical arguments in favour of randomization 'as recommended by statisticians'. However, within the constraints on space allowed me, I shall restrict my remarks to explaining why 'randomization' according to hospital number is not an acceptable procedure.

The single most compelling reason against such an allocation procedure is that it is susceptible to selection bias. The problem is that at the time that the clinician is assessing the patient for entry to the study, and eliciting informed consent, he or she is aware of the treatment to which the patient will be assigned. Almost invariably the inclusion and exclusion criteria for trials are to some extent subjective, and consciously or unconsciously the clinician is likely to be influenced by the knowledge of the treatment which the patient will receive if entered into the study. Equally, when explaining the study to the patient and obtaining consent, it is very likely that the clinician's 'sales pitch' will be influenced by the knowledge of the assigned treatment, introducing a systematic bias which means that the study does not compare like with like. Many statistical texts, for example that by Bland[1], give detailed examples of trials which have foundered precisely because of such selection biases.

This raises in passing a problem with blocked randomization as discussed by Mr Phillips. Almost by definition surgical trials are open, and so if the block size is known by the clinician then so is the treatment allocation of a number of the patients. Indeed, in a study of two treatments with a block size of two, the allocation of every second patient would be known in advance, leading to the problem of selection bias discussed above. The simple solution to this problem, but one which unfortunately is underused in practice, is to have variable block sizes. For example, in a comparison of two treatments, one might have a mixture of blocks of size four and six, and use a random mechanism to choose the length of the individual blocks.

Since true randomization is so simple to implement in practice, and since it gives such a strong defence against accusations of selection bias, there is really no excuse for adopting such poor practice as basing treatment allocation on hospital number or any other mechanism which makes the clinician aware of the allocation before the potential patient is recruited into the study.

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## Chylothorax after oesophagectomy

*Sir*

I read with great interest the paper by Professor Hennessy and colleagues (*Br J Surg* 1991; **78**: 587–8). There was a high occurrence of chylothorax in patients who underwent transhiatal oesophagectomy, where in 95 patients there was an incidence of 10·5 per cent. On the other hand, of 442 patients who underwent open thoracotomy only one developed this complication. Of the 197 patients who underwent the two-phase Lewis–Tanner procedure, none developed chylothorax. Of 99 who underwent the three-phase procedure, one patient developed this complication. In this single case it is not stated whether the cervical oesophagus was approached from the left or from the right side. Since the thoracic dissection is identical in the two- and three-stage procedures, it may well be that chylothorax occurred as a result of damage to the thoracic duct in the neck.

During the early stages of development of the three-phase technique a left-sided approach to the cervical oesophagus was carried out[1], but the dangers to the thoracic duct during delivery of the cervical oesophagus were realized. Thereafter all cervical approaches have been made on the right-hand side. This paper rightly emphasizes the dangers of chylothorax in oesophagectomy. The very high incidence following transhiatal oesophagectomy as recommended by Orringer and Orringer[2] is a contraindication to this blind procedure. Though transhiatal oesophagectomy may be acceptable for the removal of the normal oesophagus in conjunction with pharyngolaryngectomy, it seems less appropriate in cases of extensive carcinoma of the middle third of the oesophagus.

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## Node-negative breast cancer prognosis and DNA ploidy

*Sir*
The paper of Yuan and colleagues (*Br J Surg* 1991; **78**: 844–8) purports to show the long-term prognostic value of DNA ploidy in node-negative breast cancer.

Much of the paper describes data for both node-positive and node-negative patients; of the four figures and three tables, only one (*Figure 3*) illustrates the prognostic value of DNA ploidy in node-negative patients. Of 170 patients studied, 120 were node-negative. This too is confusing, as in most unbiased series of this size, this proportion of node-negative patients is unduly high. Surgery is said to be *principally* mastectomy with node sampling; did all patients have adequate node sampling?

The authors make the point that the relative prognostic importance of variables is best assessed in multivariate analysis; yet no such multivariate analyses are shown for node-negative patients alone. No account is given in the discussion of the conflicting findings of other authors who have similarly assessed the potential value of DNA ploidy in node-negative women[1–3]. In a multivariate analysis of 368 node-negative patients treated in this unit (median follow-up 8 years) neither DNA ploidy nor c-*erb*B2 were of independent prognostic value additional to histological grade or tumour size. In the analysis DNA ploidy, c-*erb*B2, menopausal status, tumour size and histological grade were entered. As Yuan found, DNA diploidy/aneuploidy was of prognostic significance in univariate analysis ($P = 0.002$).

The authors comment that identification of women with potentially poor outcome from within good prognostic groups is difficult. What is required is a pathologist who carefully measures tumour size and assesses histological grade or morphological type.

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### Authors' reply

*Sir*
We thank you for the opportunity to reply to the letter from Galea *et al.* Our paper states clearly that we examined stage I and II tumours only in our analysis. I think this readily explains the high proportion of node-negative patients. Multivariate analysis included patients who were node-negative or node-positive and it is only by including both of these variables in the analysis that one can identify whether the node-negative group fare any better than the node-positive. To analyse the node-negative patients alone would not give this information.

In our paper, 16 of the 24 references are to publications on the subject of ploidy and breast cancer, and we would consider this to be an adequate review and discussion of the findings of other authors.

We agree that careful pathological assessment of the tumour is important and indeed refer to the work of Dr Elston in our paper. We describe methods to obtain additional information to histopathological examination by using flow cytometric techniques and analysis of DNA ploidy. The data presented in our paper would support our suggestion that this can be a valuable adjunct to routine histopathology.

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## Comparison of iliofemoral and femorofemoral crossover bypass in the treatment of unilateral iliac arterial occlusive disease

*Sir*
What is the point in publishing yet another retrospective study that purports to compare iliofemoral and femorofemoral crossover bypass (Hanafy and McLoughlin, *Br J Surg* 1991; **78**: 1001–2)? The argument about which operation is best for the treatment of unilateral iliac artery occlusion has been continued for over 10 years, and this article does nothing to resolve that argument. It is impossible to compare two operations retrospectively as patient selection is bound to be different. This is particularly the case with these two operations, as selection for iliofemoral bypass depends on the presence of a patent ipsilateral common iliac artery. If it is occluded, then a crossover bypass would be required. Unfortunately, the authors have failed to tell us how many patients were actually suitable for either operation.

The authors conclude in their abstract and discussion that iliofemoral bypass is superior because it avoids a groin incision in the donor limb, leaving the common femoral artery intact for subsequent angioplasty if required. This problem can be avoided if the contralateral external iliac artery is used as the donor vessel rather than the common femoral artery[1]. This technique is mentioned briefly in the introduction, so why have the authors not adopted it?

The only way to resolve the argument over these two operations is a prospective randomized trial. A multicentre trial was started by the Joint Vascular Research Group over 2 years ago, but recruitment has been poor, although these operations are commonly performed. If more surgeons were prepared to enter their patients into simple multicentre studies, then questions such as this could be easily answered, and vascular surgery in this country might advance more rapidly.

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### Authors' reply

*Sir*
We thank Mr Beard for his interest in our paper. We mentioned in the *Patients and methods* section that a total of 74 patients with unilateral iliac arterial occlusive disease were 'randomly allocated' to either an iliofemoral or a femorofemoral crossover bypass procedure between March 1981 and December 1988. This indicates that the study was prospective rather than retrospective.

We indicated as well that the criteria for selection for a crossover bypass were: a strong femoral pulse in the asymptomatic leg, an absent or grossly reduced pulse in the symptomatic leg, and angiographic confirmation of occlusive iliac disease not amenable to angioplasty or a failed attempt at previous iliac angioplasty on the symptomatic side. All patients were required to receive a crossover bypass. No special selection criteria were considered for a patient to receive an iliofemoral rather than a femorofemoral bypass graft. All patients were suitable to undergo either operation. The question was as to which type: an iliofemoral crossover or a femorofemoral crossover bypass graft?

Unilateral (ipsilateral) iliofemoral bypass performed between the common iliac and the common femoral arteries on the same side was not an issue discussed in this study.

We could not adopt any technique since patients were randomly allocated to either group, as mentioned before.

We feel that the outcome of this trial indicates that both operations lead to the same result and that the difference in the technique to approach the donor vessel above rather than below the inguinal ligament could offer, if adopted, certain advantages.

**M. Hanafy**
**G. A. McLoughlin**

*Department of Vascular Surgery*
*Royal Liverpool Hospital*
*Liverpool L7 8XP*
*UK*

## Bleeding pseudocysts and pseudoaneurysms in chronic pancreatitis

*Sir*

We read with interest the article by Hamel *et al.* (*Br J Surg* 1991; **78**: 1059–63). This provided an excellent review of an interesting and serious complication of chronic pancreatitis. However, no mention was made of erosion of the aorta by a pseudocyst, a complication of pseudocyst formation we have recently experienced. We believe that in such a case a policy of pancreatic resection, as suggested by the authors, would not be advisable.

A 66-year-old woman with a history of chronic pancreatitis and a pancreatic pseudocyst in the head of the pancreas causing jaundice (in whom there was no coagulopathy) underwent cystgastrostomy. On the seventh day after operation she had two substantial haematemeses. Gastroscopy was attempted but the stomach was full of blood. In view of continued bleeding, the abdomen was reopened. No bleeding point could be found in the stomach but the cyst was distended with clotted blood. The clot was removed to reveal torrential bleeding from the side wall of the aorta. This was controlled by oversewing with interrupted silk sutures. She made an uneventful recovery and was eventually discharged home on the 18th day after operation.

Although the aorta is an immediate anatomical relation of a pseudocyst, it is surprising that there have been few reports of erosion of this vessel. We feel that this source should be considered when dealing with a case of upper gastrointestinal haemorrhage in a patient with chronic pancreatitis.

While it is suggested that primary pancreatic resection be undertaken in these patients, this would obviously have been inappropriate in this case where the operation had to be swift and unrefined.

**N. A. Burgess**
**M. W. Scriven**
**M. H. Lewis**

*East Glamorgan General Hospital*
*Church Village*
*Mid Glamorgan*
*UK*

## No abdominal drainage after Whipple's procedure

*Sir*

After Whipple's resection one or two drains are usually left in the upper abdominal cavity. This practice is based on the concept that postoperative leakage of blood, bile and pancreatic secretion may occur and that the consequences of this leakage may be reduced by leaving a drain. Drains are placed in the area around the pancreaticojejunostomy and choledochojejunostomy, anticipating possible leakage from these anastomoses. Often the drain is left *in situ* for a few days as leakage may occur 4–7 days after operation. It is questionable whether this drainage procedure is effective. Anastomotic leakage is a well known problem after Whipple's procedure, but one that should affect less than 10 per cent of patients in experienced hands. If leakage occurs, a drain may not be useful as a diagnostic tool or therapeutic method and might even be hazardous as it creates a pathway for contamination. Often the drain is obstructed within a few days or separated from the anastomotic area by omentum or adhesions.

From 1989 until September 1991 an intra-abdominal drain was omitted after Whipple's resection in 22 patients. In 14 patients operated on in the same period a drain was positioned after Whipple's resection because of diffuse bleeding or because a different surgeon performed the operation, but these cases are not considered further.

Resection of the pancreas was performed for carcinoma of the head of the pancreas ($n = 12$), periampullary cancer ($n = 5$), villous adenoma of the duodenum or pancreatic duct ($n = 2$) and chronic pancreatitis ($n = 3$). The age of the patients varied from 43 to 79 years. In all cases a single layer anastomosis was performed for pancreaticojejunostomy and choledochojejunostomy. A pylorus-preserving Whipple operation was performed in 20 patients.

An abdominal abscess was noted after operation in three patients, but this could be treated without operative drainage. A drain was placed in the abscess by ultrasonically guided puncture in one case. In none of the 22 patients was there a need for relaparotomy to drain an intra-abdominal abscess. Reoperation was performed in one patient because of wound dehiscence. No patient died in the postoperative admission period. Patients were discharged from hospital at a mean of 18·5 (range 8–55) days.

In conclusion, postoperative drainage after Whipple's procedure may be omitted without undue complications.

**J. Jeekel**

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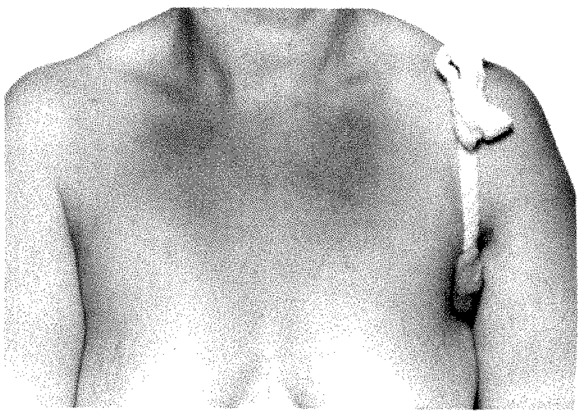
*The Netherlands*

## Staphylococcal infection of hidradenitis excisions

*Sir*

Our wound clinic has previously described a series of 50 axillary skin excisions for suppurative hidradenitis (*Br J Surg* 1987; **74**: 95–7). Of these, 17 suffered staphylococcal infection attributed to friction by the Silastic® foam (Dow Corning, Reading, UK) used as a dressing and held in place by adhesive tape. Many patients develop allergy to such tape. To avoid this problem we have in recent years included in the Silastic foam (as it is setting) a length of elastic net (Surgifix no. 3, 2 cm width). The free ends of the net are tied to the brassière strap for women and taken round the neck for men. An unexpected benefit from this procedure has been the elimination of friction and staphylococcal infection. The elasticity of the net allows the dressing to accommodate to arm movement without undue pressure on the wound in contrast to the non-compliance of the adhesive tape previously used.



*The dressing sling shown before attachment to the brassière strap*

**J. Marks**

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*UK*

## Gynaecomastia

*Sir*

I enjoyed reading the review by Hands and Greenall (*Br J Surg* 1991; **78**: 907–11) on gynaecomastia. However, on a global scale (and especially with the worldwide distribution of *The British Journal of*

*Surgery*) perhaps specific mention could have been made of gynaecomastia occurring in 18–36 per cent of cases of lepromatous leprosy[1–3] There are today approximately 12–15 million people suffering from leprosy throughout the world (personal communication from National Hansen's Disease Registry, Carville, Louisiana, USA) amongst whom testicular involvement and damage is common[4]. The reason for this is possibly the preference of the organism for cooler areas of the body (and thus, also, peripheral nerves)

**A. Stacey-Clear**

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1. El-Shiemy S, El-Hefnawi H, Abdel-Fattah A, El-Okbi M, Farrid A. Testicular and epididymal involvement in leprosy patients, with special reference to gynaecomastia. *Int J Dermatol* 1976; **15**: 52–8
2. Grabstald H, Swan LL. Genitourinary lesions in leprosy with special reference to the problem of atrophy of the testis. *JAMA* 1952: **149**· 1287–91.
3. Kumar B, Raina A, Kaur S, Dash RJ, Samuel E, Datta BN. Clinicopathological study of testicular involvement in leprosy. *Lepr India* 1982, **54**: 48–55.
4. Desikan KV, Job CK. Visceral lesions caused by *M. leprae*· a histopathological study. *Indian J Pathol Bacteriol* 1970; **13**: 100–8.

## Justifying arterial reconstruction to crural vessels – even with a prosthetic graft

## and

## New prosthetic venous collar anastomotic technique: combining the best of other procedures

*Sir*
We read with interest both the Leading Article (*Br J Surg* 1991, **78**· 897–9) and the Surgical Workshop article (*Br J Surg* 1991; **78** 1016–17) by Messrs Wolfe and Tyrrell

Contrary to the statement in the Leading Article, we first developed our anastomotic vein patch technique in 1982 rather than in 1988[1–3]. The results of an 8-year follow-up, in which 256 patients with femoropopliteal and femorodistal bypass grafting were reviewed, have recently been submitted to your journal for publication[4]. Cumulative primary patency rates for 83 tibioperoneal grafts of 74 per cent, 58 per cent and 54 per cent were achieved at 1, 3 and 5 years respectively. We remain unconvinced as to the value of short-term results and for this reason have previously published only summarized figures until there are an adequate number of patients with a 5-year follow-up.

We would take issue with the authors' comments in the discussion of the paper relating to their new venous collar anastomotic technique. While it is true that our technique does involve a short length of direct polytetrafluoroethylene–arterial anastomosis, there is no evidence whatsoever that this increases the risk of intimal hyperplasia or premature graft occlusion. Indeed, the available clinical results would suggest that the contrary is true. The results reported by Tyrrell *et al.*[5] with the Miller collar in femorodistal bypass show a 33 per cent 1-month occlusion rate and a 73 per cent 1-year occlusion rate, although these results were not cumulative. Seventy per cent (21) of the patients avoided amputation, but of these four underwent immediate thrombectomy, three underwent revisional surgery (of which one was due to disruption of anastomosis) and a further five patients had occluded grafts but did not require further intervention to maintain limb viability.

Although improved results have been obtained with the Miller cuff in bypass grafting to crural vessels (52 per cent patency rate, presumably secondary, at 3 years in 55 cases according to the Leading Article), controversy still exists as to the technique that would achieve better results. This could be resolved only by a prospective randomized trial involving the Miller cuff and the Taylor patch. However, the authors have further confused the issue by publishing in their Surgical Workshop a new technique with no results. We feel it is dangerous that such a technique be recommended without further information about even short-term results.

**R. S. Taylor**
**J. A. Dormandy**

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*London SW17 0QT*
*UK*

1. Taylor RS, McFarland RJ, Cox MI. An investigation into the causes of failure of PTFE grafts. *Eur J Vasc Surg* 1987; **1**· 335–43.
2. McFarland RJ, Taylor RS. Une amelioration technique d'anastomose des protheses arterielles femoro-distales. *Phlebologie* 1988, **41**: 229–33.
3. Taylor RS. An investigation into the causes of failure of PTFE grafts and new techniques to improve patency *Jacksonian Dissertation Prize, Royal College of Surgeons of England*, 1986.
4. Taylor RS, McFarland RJ, Loh A, Cox M, Chester JF Improved technique for polytetrafluoroethylene bypass grafting: long-term results using anastomotic vein patches *Br J Surg* 1992, (in press)
5. Tyrrell MR, Grigg MJ, Wolfe JHN. Is arterial reconstruction to the ankle worthwhile in the absence of autologous vein? *Eur J Vasc Surg* 1989; **3**: 429–34.

### Authors' reply

*Sir*
We are grateful to Messrs Taylor and Dormandy for their comments, since they should help clarify some of the issues related to crural anastomoses using a prosthetic graft. It was the excellence of the results reported by Miller and Taylor using different techniques that stimulated our own interest. We are, of course, aware of the excellent results obtained using the Taylor patch, and Mr Taylor was a co-author of our publication which attempted to unravel the reasons for this success

It is well established that a major cause of polytetrafluoroethylene (PTFE) graft failure is myointimal hyperplasia at the distal anastomosis. We have now shown that this process occurs between the graft and the vein collar rather than in the small distal artery. It is not unreasonable to assume that myointimal hyperplasia occurs at any distal anastomosis between PTFE and autologous tissue It is, therefore, incumbent after the proponents of the Taylor patch to show that the heel of their graft is not affected in this way. Retrograde flow is particularly important when the anastomosis is at the level of the ankle, since this flow reduces resistance and allows perfusion of the calf.

We entirely agree that it is impossible to compare results between two techniques when the patients in the study are heterogeneous Thus any comparison is invalid on the current data We fully concur that this situation could be resolved by a prospective randomized trial involving the Miller collar and Taylor patch; indeed, we proposed this to them. Suffice it to say that we were unable to achieve *any* worthwhile patency for grafts longer than 70 cm to crural vessels without the use of the vein collar, and with its use have achieved a patency rate of 52 per cent at 3 years.

We are not suggesting that our collar is a 'new technique' – we merely modified the Miller collar following our studies For those who have found the Miller collar to be of benefit, it is certainly not 'dangerous' to suggest this variation in technique since the essential features are identical The only advantage is the reduction of turbulence at the toe of the anastomosis

Finally, we would like to re-emphasize that PTFE should be used only following an extensive search for autologous vein from either arm or leg. Current results do not justify the use of PTFE if autologous vein is available.

**J. H. N. Wolfe**
**M. Tyrrell**

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## Abdominal wall dehiscence following Ramstedt's operation

*Sir*
We were as concerned regarding the unseemly high incidence of both wound infections and disruptions following pyloromyotomy (*Br J Surg* 1991; **78**: 81–2) as many of your respondents (*Br J Surg* 1991, **78**: 761–2). We agree with most of the comments of your respondents regarding layered closure technique, utilization of fine, absorbable, synthetic sutures, and deprecation of chromic catgut sutures.

Unfortunately, no data have been proffered regarding a suitable current wound disruption and/or infection rate following pyloromyotomy. Stimulated by the original article, we have reviewed 153 consecutive cases treated at this centre over the past 4 years. All operations were performed by surgical house officers (usually at the junior level) directly supervised by one of two paediatric surgeons or two general surgeons on call. The abdominal wall incision was either rectus muscle splitting between taenia, or gridiron. Layered closure with fine, synthetic absorbable sutures was used consistently. Subcuticular wound closure with fine, absorbable, synthetic suture was standard. A superficial wound infection developed in one infant (0·5 per cent), there were no wound dehiscences or eviscerations.

We note that the late Dr Clifford Benson reported in 1979 one wound disruption in 1573 patients (0·06 per cent)[1]. We suggest that any incidence of wound disruption following pyloromyotomy greater than that of Dr Benson or wound infection rate more than 1 per cent should be viewed askance, and that corrective measures be instituted forthwith.

**J. J. White**
**H. G. Andrews**
**B. Branson**
**S. Cemaj**
**M. Rodgers**

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1. Benson CB. Infant hypertrophic pyloric stenosis. In: Ravitch MM, Welch KJ, Benson CD, Aberdeen E, Randolph JG, eds. *Pediatric Surgery* 3rd ed. Chicago. Year Book Medical Publishers, Incorporated, 1979: 894

## Quadrantectomy for early breast cancer

*Sir*
We have three comments to make regarding Mr Young's recent Leading Article (*Br J Surg* 1991, **78**: 387). The first is that the author indicates that the success of quadrantectomy in prevention of local recurrence may be in part related to the anatomical wedge of tissue that is removed. It should be clearly understood that the breast is not made up of segments which can be neatly excised by the surgeon and there can be no certainty in a quadrantectomy that the duct or ducts draining a portion of breast tissue have been excised in such a resection.

The second point relates to the interpretation of the results of the comparison of quadrantectomy and lumpectomy reported by Veronesi *et al*[1]. In this study there were 24 local recurrences in the lumpectomy group and eight in the quadrantectomy group; six of the recurrences in the lumpectomy group occurred in patients with extensive *in situ* disease – a known risk factor for local recurrence[2] – and a further six patients had incomplete excision of their primary tumour. Thus, there were only 12 patients in whom local recurrence might not have been expected. In the quadrantectomy group, only one of the eight local recurrences could be explained either by extensive *in situ* disease or carcinoma at the resection margins. The difference in unexpected recurrences between the two groups is, therefore, 12 in the lumpectomy group *versus* seven in the quadrantectomy group, which is not statistically significant. Of importance, ten of the 24 patients with recurrence after lumpectomy were salvaged by quadrantectomy, and the recurrences in the lumpectomy group were not associated with a worse survival. It is also clear from the Veronesi paper that the cosmetic results from lumpectomy were significantly better than those for quadrantectomy, but there was no comment of this in Mr Young's article.

The third area of contention is the interpretation of the results of the NSABP study, a randomized trial which compared total mastectomy and lumpectomy with or without breast irradiation[3]. Mr Young reports that this study shows that the adequacy of local excision is crucial in minimizing the incidence of local recurrence. The *Methods* section of this paper states that all resected specimens from patients who underwent lumpectomy were examined histologically and any patient with involvement of the margins underwent total mastectomy. As there were no patients in the study with involved margins who underwent local excision, we fail to see how Mr Young draws any conclusion relating adequacy of local excision and recurrence from this study.

The reason that patients develop recurrence after local excision is clearly multifactorial, and the extent of surgery is one of many inter-related factors. To determine whether quadrantectomy is superior to wide local excision, a study would have to take these various factors into account when the data are analysed. No study to date has done this, and we would suggest, therefore, that the question of whether quadrantectomy is superior to an adequate wide local excision has yet to be proven.

**J. M. Dixon**
**U. Chetty**
**A. Rodger**

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*The Royal Infirmary*
*Edinburgh EH3 9YW*
*UK*

1. Veronesi U, Volterrani F, Luini A *et al.* Quadrantectomy *versus* lumpectomy for small size breast cancer. *Eur J Cancer* 1990; **26**: 671–3.
2. Schnitt SJ, Connolly JL, Harris JR, Hellman S, Cohen RB. Pathologic predictors of early local recurrence in stage I and II breast cancers treated by primary radiation therapy. *Cancer* 1984; **53**: 1049–57.
3. Fisher B, Redmond C, Poisson R *et al*. Eight-year results of a randomized clinical trial comparing total mastectomy and lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med* 1989, **320**: 822–8.

### Author's reply

*Sir*
The purpose of a Leading Article is to stimulate debate and I am pleased that the article on quadrantectomy achieved that end. Its purpose was merely to draw readers' attention to a report showing excellent results from conservative therapy for breast carcinoma at a time when some other papers published in *The British Journal of Surgery* had indicated a contrary view. I am no better able than Messrs Dixon, Chetty and Rodger to explain the excellence of the results of Veronesi *et al*, and the debate therefore needs to be kept open, not closed.

**A. E. Young**

*St. Thomas' Hospital*
*London SE1 7EH*
*UK*

## Rebound tenderness test

*Sir*
Liddington and Thomson (*Br J Surg* 1991, **78**: 795–6) are to be congratulated on their analysis and condemnation of this test which I have long taught constitutes 'cruel and unusual punishment'.

I believe that the most important procedure in the 'doubtful abdomen' is repeat examination by the same doctor after an interval of a few hours when the patient will have gained confidence in his or her surroundings and the doctor. Trust in the doctor can too easily be destroyed by using this unreliable sign which is 'simply a more dramatic way of demonstrating tenderness and rigidity'. Drama has no place in the initial (nor any other) examination of a patient with abdominal pain. How long will it be before this test can be expunged from our teaching and practice?

**W. A. Anderson**

*Derbyshire Children's Hospital*
*North Street*
*Derby*
*UK*

# Book reviews

## Inflammatory Bowel Disease Diagnosis and Treatment

*G Gitnick (ed.). 261 × 181 mm. Pp. 544 + xix. Illustrated 1991. USA Igaku-Shoin.*

In the preface the Editor claims that this book 'fills a need for an up to date clinical and concise overview of inflammatory bowel disease'. I think he probably is correct, that there is such a need, and that the book largely satisfies it. It is comprehensive and provides a wealth of well referenced information on most aspects of ulcerative colitis and Crohn's disease. A number of recognized authorities, from both sides of the Atlantic, have contributed to the text. It is well presented with sections on aetiology and epidemiology, clinical features, diagnosis, prognosis, medical management, surgical management and problems in management. The book appears to be aimed more towards the medical gastroenterologist, although surgeons with a particular interest in the management of these difficult conditions will find it a useful, well referenced, text.

The large first section on the aetiology and epidemiology of inflammatory bowel disease contains an excellent chapter reviewing the historical developments in both ulcerative colitis and Crohn's disease. There is an extensive coverage of the medical management of inflammatory bowel disease, with chapters written on each of the drugs constituting the routine armamentarium of the medical gastroenterologist, as well as chapters on the more recent advances in medical treatment such as the role of cyclosporin A and T lymphocyte plasmaphaeresis

Compared with the large amount of space allocated to medical management, the coverage of the surgical management of these diseases is paltry Surgeons seeking technical guidance and illustrated details of the operative techniques involved in the more recent surgical developments must look elsewhere

There are some excellent radiographic illustrations in the section on diagnosis of the disease, but throughout the book illustrations are not abundant. Although there are a few high quality endoscopic colour plates, many of the endoscopic illustrations are in black and white and therefore lose a great deal of their impact

In general, I feel that this book will prove to be a worthwhile addition to the literature about inflammatory bowel disease, providing a useful referenced text, though not one written primarily for the surgeon.

**A. Berry**

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*Billing Road*
*Northampton*
*UK*

## Debates in Clinical Surgery. Vol. 2

*R. L Simmons, A O. Udekwu (eds.). 152 × 229 mm Pp. 245. Illustrated. 1991. USA Mosby Year-Book Inc £37*

This second volume attempts to address a series of current surgical topics, some long-standing and others more recent. As the Authors say in their preface, obviously the standard of debate relates critically to the quality of the authors selected to put forward the case for or against a particular treatment

In general the book succeeds well with its chosen aim The topics are timely and almost all are of concern to surgeons, whether practising in academic units in large hospitals or in district general hospitals.

Inevitably the pace of medical advance has meant that some topics have been left behind This applies to the first on cholecystectomy, where the time taken to get to printing has meant that the great surge of interest in laparoscopic cholecystectomy has really not been adequately covered The section on venous thromboembolism is not a debate, but is included as a plea for surgeons everywhere to be more conscious of the need to apply preventive measures, and warns of the risk of litigation if this is not done The chapter on the controversies about the Angelchik prosthesis is a fair debate, producing evidence for and against the new method of controlling reflux oesophagitis. It is also timely, in that initial enthusiasms were replaced by a violent reaction against the device because of isolated case reports of nasty complications. More recently, as the authors conclude, a more balanced view is developing of the place of the device in the range of procedures available for antireflux surgery. The section on colonic pseudo-obstruction is a less satisfactory debate in that the second author seems not to have considered the possibility of colonoscopic decompression at all in his management protocol Perhaps one of the more important debates is that on the extent of the surgical procedure for pancreatic cancer. It is well presented both for and against an increasingly radical procedure for the resection and, along with an extensive reference list, should provide further fuel for the debate in the future. I would hope that future volumes will address the question of whether preoperative decompression by the endoscopic insertion of biliary endoprosthesis may improve the results, and also whether endoscopic decompression is better for palliation than surgical bypass.

In conclusion, this volume should be of value on the shelf of any library or office both to surgeons already in clinical practice and perhaps particularly for surgeons in training.

**M. W. L. Gear**

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*UK*

## Atlas of Breast Reconstruction

*L. Vasconez, M. LeJour, M. Gamboa-Bobadilla. 260 × 190 mm. Pp. 264. Illustrated 1990. Philadelphia. J B Lippincott. $129 50*

Another book about breast reconstruction raises the questions, who is it for and what is different about it? The Authors, two from Alabama and one from Belgium, have with their contributions managed something a little different but I remain uncertain about their audience The beginner will find he or she needs an extensive grounding in basic technique, the expert will find much of it too much part of everyday work.

The book approaches the subject on a technique-by-technique basis so that it is strong on technical matters but weak when it comes to selecting the best technique for a problem The 16 chapters cover reconstruction with implants and expanders, latissimus dorsi flap reconstruction, rectus abdominis flaps, procedures on the opposite breast, nipple areolar reconstruction, secondary problems, complications and types of implant.

Like most books from plastic surgeons, it is extensively illustrated with line drawings and clinical photographs. Many of these are excellent but some are frankly confusing This is not helped by the absence of legends and the fact that the relevant text and the illustrations are sometimes on different pages.

Five chapters are well referenced although for a book published in 1990 rather elderly; other chapters are anecdotal and have no references at all. There is no index, so finding the many good ideas in this book is not as easy as it might be The strengths of this book are its technical sections and its dealing with the problems. The weaknesses lie in selection of appropriate procedures and the discussion on indications This book will find a place in plastic surgery theatres and is a useful addition to the literature on breast reconstruction My criticism perhaps reflects my regret that this book does not quite make that greater leap from being good to being outstanding.

**D. Webster**

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# Notices and announcements

24 March 1992
**Study Day on Management of Pancreatic Cancer**
*Southampton, UK*
*Information* Mrs J Daniels, University Surgical Unit, F Level Centre Block, Southampton General Hospital, Tremona Road, Southampton SO9 4XY, UK

29 March–2 April 1992
**29th Annual Meeting – Controversial Areas in General Surgery**
*Palm Springs, California, USA*
*Information* Health Sciences, UCLA Extension, 10995 Le Conte Avenue, Room 614, Los Angeles, CA 90024, USA

30 March–4 April 1992
**Head and Neck Oncology: Current Issues and Recent Advances**
*London, UK*
*Information* Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

1–3 April 1992
**Association of Surgeons of Great Britain and Ireland Annual Meeting**
*Jersey, UK*
*Information* Ms Caroline Ross, The Royal College of Surgeons, 35/43 Lincoln's Inn Fields, London WC2A 3PN, UK

13–14 April 1992
**Injury Research Group 1992 Meeting**
*Manchester, UK*
*Information* Dr R. N Barton, North Western Injury Research Centre, Stopford Building, University of Manchester, Oxford Road, Manchester M13 9PT, UK

13–15 April 1992
**1st Portuguese–Spanish International Meeting on Colorectal Pathology**
*Lisbon, Portugal*
*Information* Dr António Castro Mendes de Almeida, University Hospital of Santa Maria, Medicina Operatória, Piso 2, 1699 Lisbon Codex, Portugal

22–25 April 1992
**Updating Course on Pancreatic Diseases**
*Genoa, Italy*
*Information*. Organizing Secretariat, QB Service, Via Visconti Venosta 4, 21122 Milano, Italy

22–25 April 1992
**2nd International Workshop and Symposium on Therapeutic Endoscopy and Gastroenterology**
*Shanghai, China*
*Information* Dr J. W. C Leung, Department of Medicine, Prince of Wales Hospital, Hong Kong

3–7 May 1992
**7th International Congress on Senology (Breast Diseases) of the Senological International Society**
*Rhodes, Greece*
*Information* Congress Secretariat, 102 Michalakopoulou Street, GR-115 28 Athens, Greece

5 May 1992
**Surgery in the Developing World – The Challenge to Britain**
*London, UK*
*Information* Keith Newton, Royal Society of Medicine, 1 Wimpole Street, London W1M 8AE, UK

10–16 May 1992
**Acute Trauma Management**
*Belfast, UK*
*Information* Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

15 May 1992
**Abdominal Aortic Aneurysms – Assessment and Management**
*Ayr, UK*
*Information* Mr G. Stewart, The Ayr Hospital, Dallmington Road, Ayr KA6 6DX, UK

17–23 May 1992
**Recent Advances in Endocrinology and Metabolism**
*Edinburgh, UK*
*Information* Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

20–23 May 1992
**83rd Meeting of the American Association for Cancer Research**
*San Diego, California, USA*
*Information* American Association for Cancer Research, Inc, Public Ledger Building, 620 Chestnut Street, Suite 816, Philadelphia, PA 19106-3483, USA

27–29 May 1992
**European Council for Coloproctology Fourth Biennial Congress**
*Marseille, France*
*Information* Patricia Vallet, Alice Congrés, 12 Cours Jean Ballard, BP 2028 13201 Marseille cedex 01, France

2–5 June 1992
**Eurochirurgie '92 2nd European Congress of Surgery**
*Brussels, Belgium*
*Information* Congress Secretariat: Eurosurgery '92, Brussels International Trade Fair, Place de Belgique, B-1020 Brussels, Belgium

7–10 June 1992
**International Congress on Cancer of the Esophagus**
*Genoa, Italy*
*Information* Secretariat, Luigina Bonelli, Unit of Clinical Epidemiology and Trials, Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy

7–11 June 1992
**4th World Congress of Hepato-Pancreato-Biliary Surgery**
*Hong Kong*
*Information* Secretariat, International Conference Consultants Ltd. Suits A and B, 16/F, Casey Building, 38 Lok Ku Rd, Sheung Wan, Hong Kong

9–10 June 1992
**Specialist Short Course: New Trends in Pathology**
*London, UK*
*Information* J. Ashton, Wolfson Conference Centre, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

15–19 June 1992
**Specialist Short Course: Advances in Haematology**
*London, UK*
*Information* J Ashton, Wolfson Conference Centre, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

24–27 June 1992
**The Endocrine Society 74th Annual Meeting**
*San Antonio, Texas, USA*
*Information*· Ann Singer, The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814, USA

28 June–3 July 1992
**4th Oxbridge Organ Transplantation Course**
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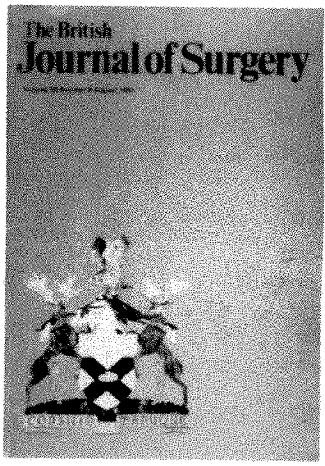

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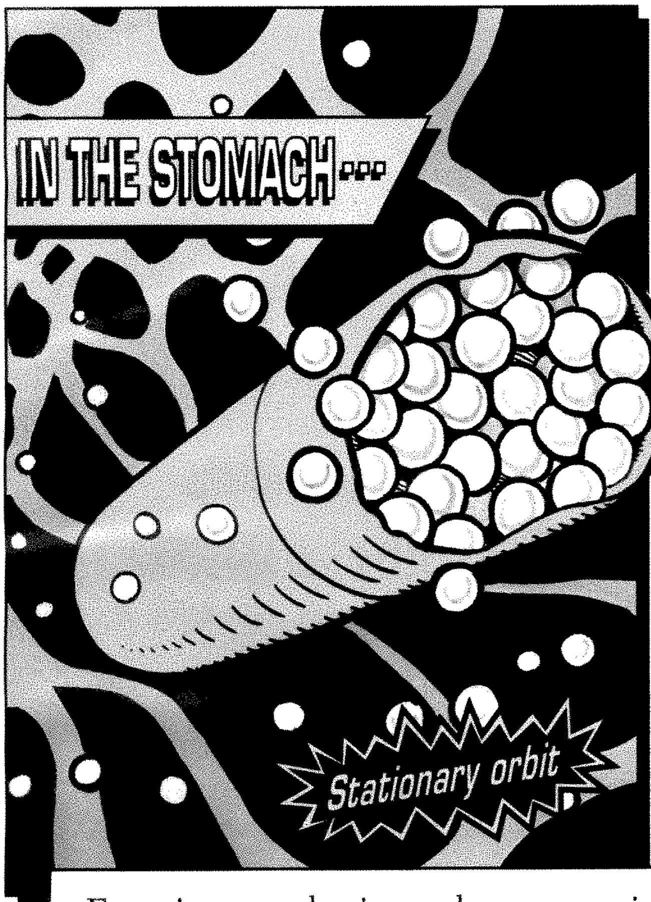

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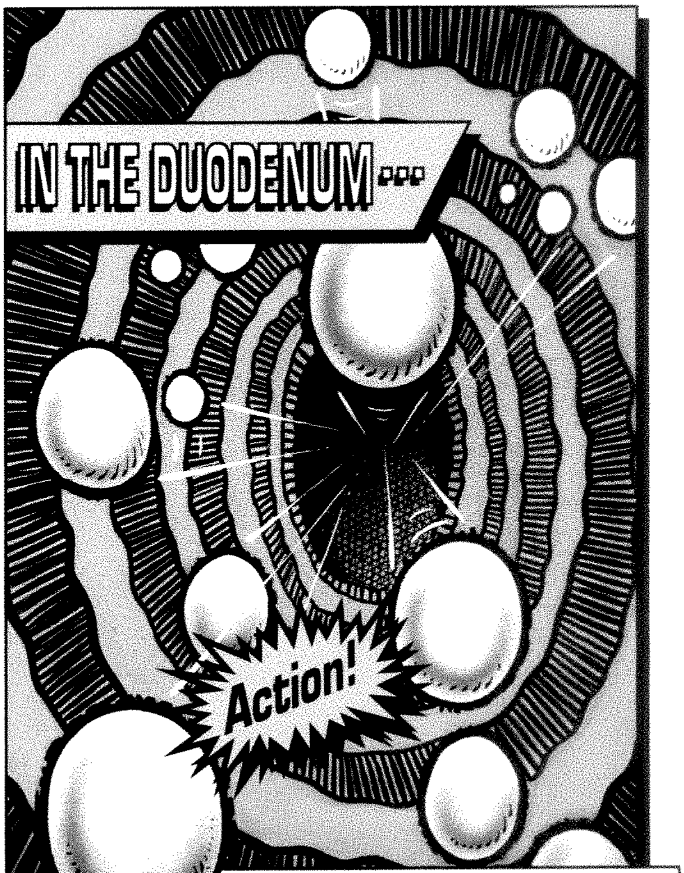
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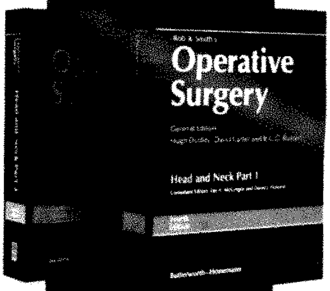

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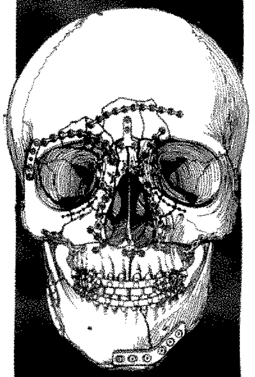

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# Editorial Committee of The British Journal of Surgery

Br. J. Surg. 1992, Vol. 79,
September, 857–858

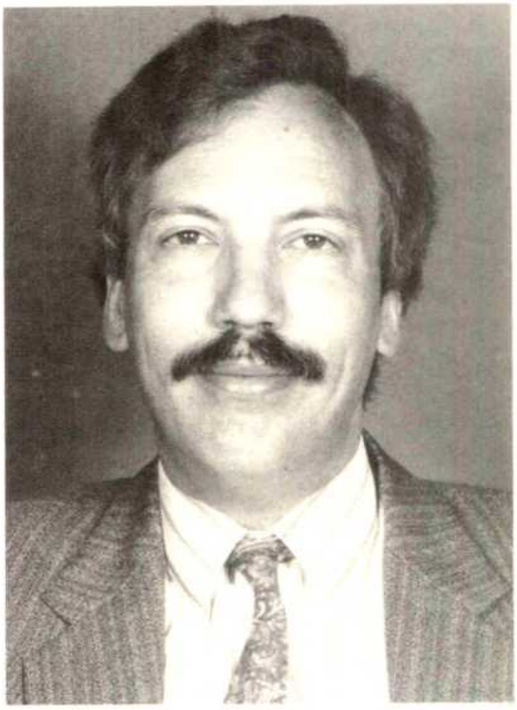
*In recent months we have presented the Members of Council of The British Journal of Surgery Society, the body that owns and administers the Journal, and we now conclude Council and continue with the other Members of the Editorial Committee.*

## New Members of Council from 1992

### PROFESSOR TIMOTHY COOKE

Timothy Gordon Cooke is St Mungo Professor of Surgery in the University of Glasgow and a consultant surgeon at Glasgow Royal Infirmary. He was born in 1947 and qualified at Liverpool in 1973, working in the Merseyside Region until 1980 when he became Lecturer in Surgery at Southampton. Tim Cooke became a consultant senior lecturer first at Charing Cross Hospital (1983–1986) and then at the Royal Liverpool and Broadgreen Hospitals (1986–1989) before being appointed to his present post in succession to Professor David Carter in 1989. While travelling the country in this way he has acquired several awards and distinctions: FRCS (Eng) in 1977, MD (Liverpool) in 1980, a Hunterian Professorship of The Royal College of Surgeons in 1980, the Helen Tomlinson Cancer Research Scholarship in 1981 and the James IV Travelling Fellowship in 1991. Professor Cooke's several clinical and research interests include surgical oncology, notably breast and colorectal cancer, and endocrine surgery, notably thyroid and parathyroid. Unnumbered in his curriculum vitae, his publications are too numerous to count. He joined the Editorial Board of *The British Journal of Surgery* in 1991 and the Editorial Committee and Council this year.

### MR RICHARD SAINSBURY



John Richard Cochrane Sainsbury is a consultant surgeon at Huddersfield in Yorkshire. Born in 1954, he qualified at the University of Newcastle upon Tyne Medical School where he was awarded the Gibb Scholarship and was Captain of Athletics. After qualifying, he worked as a house surgeon at the Royal Victoria Infirmary, Newcastle. His surgical training from senior house officer through to senior registrar continued in and around Newcastle. He obtained the FRCS in 1981 and an MD with distinction in 1986. He won both the Patey Prize (Surgical Research Society) and the Raven Prize (British Association of Surgical Oncology), together with the David Dickson Research Award. His main clinical interest is in breast disease, and he has written numerous papers and book chapters on this subject. A glimpse of his leisure activities is provided by the discovery that he holds the Mountain Leadership Certificate and has been Medical Director of the Great North Run: hence one particular publication entitled 'Beta-endorphin – a factor in fun run collapse?' He joined the Editorial Board of *The British Journal of Surgery* in 1991 and the Editorial Committee and Council this year.

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## DR GORDON MURRAY

Gordon Douglas Murray is Statistical Consultant to the Journal, a position he has held since 1989. Born in 1953 he was educated at Trinity College Cambridge, where he obtained a Diploma in Mathematical Statistics with distinction, and then at Glasgow University, where he obtained a PhD (in 1979). Since 1977 he has been successively Research Assistant, Lecturer, Senior Lecturer and now Reader in Medical Statistics at Glasgow. His introduction to medicine was an appointment to the Department of Neurosurgery, and he has since been heavily involved in the organization of clinical trials. On behalf of the Journal he looks at all papers in which the Editors or referees have any concern regarding the statistical analyses. Potential contributors who are uncertain about which statistical test to use or how to present their numerical data would be well advised to read his recent publications in the Journal:

The task of a statistical referee. *Br J Surg* 1988; **75**: 664–7.

Statistical aspects of research methodology. *Br J Surg* 1991; **78**: 777–81.

Statistical guidelines for *The British Journal of Surgery*. *Br J Surg* 1991; **78**: 782–4.

## MR ADRIAN MARSTON

Jeffrey Adrian Priestley Marston was born in 1927 and educated at Oxford and St Thomas' Hospital Medical School. He qualified as a doctor in 1951 and subsequently obtained FRCS (Eng) in 1958 and DM MCh (Oxon) in 1964. He became a consultant surgeon at the Middlesex Hospital, London, and was also appointed to the staff of the Royal Northern Hospital, Manor House Hospital, and the Royal National Orthopaedic Hospital, London. Adrian Marston's major clinical interest is in vascular surgery. The number and variety of his honorary society memberships attest to his gifts as a linguist as well as his surgical distinction. At home he has been President of the Association of Surgeons of Great Britain and Ireland, and became Vice-President of The Royal College of Surgeons of England in 1991. He joined the Editorial Committee of the Journal in 1987 and served on Council from 1989 to 1992. Together with Professor Cristobal Pera of Barcelona he has been largely instrumental in establishing the Spanish edition of the Journal.

## MR TONY YOUNG

Mr Anthony Elliott Young was born in 1943 and educated at St John's College Cambridge and St Thomas' Hospital Medical School. He qualified in 1968, obtained his FRCS (Eng) in 1973 and MChir (Cantab) in 1979. His surgical training took place in and around London, based on St Thomas' Hospital but with a year at the Peter Bent Brigham Hospital, Boston, USA. He was appointed consultant surgeon at St Thomas' Hospital, London, in 1981 and is presently Director of Surgery at that hospital. Although Tony Young has written on a wide variety of clinical topics, his major interests lie in endocrine and breast surgery. He joined the Editorial Board of The British Journal of Surgery Society in 1984, acting as Assistant Editor of the Journal until 1986 and then as Associate Editor until 1988. He took a particular interest in the computerization of the editorial office. He served on the Council of the BJS Society from 1986 to 1991 before he reverted to being an 'ordinary' Member of the Editorial Committee last year.

**Robin Williamson**

Leading articles

Br. J. Surg. 1992, Vol. 79, September, 859–860

# Non-surgical management of the acute variceal bleed

Although oesophageal varices account for approximately 10 per cent of all presentations with upper gastrointestinal haemorrhage, the associated mortality rate of between 30 and 40 per cent makes variceal bleeding one of the most formidable emergencies in medicine today. The principles of management of the acute bleed are exactly the same as those for other forms of upper gastrointestinal haemorrhage, namely resuscitation, diagnosis and measures to stop the bleeding, which initially are non-operative. In approximately 30–40 per cent of patients the varices are actively bleeding, in some cases torrentially, at the time of diagnostic endoscopy. In these patients urgent resuscitation and treatment are essential to prevent death from hypovolaemic shock. Even in those patients in whom bleeding has temporarily ceased, early treatment is essential since continued or recurrent bleeding will precipitate hepatic encephalopathy, hepatorenal syndrome and further derangement of an already abnormal coagulation profile.

Since 1975 it has become increasingly clear that emergency injection sclerotherapy is a most effective treatment for controlling the acute variceal bleed. One course of injection sclerotherapy will control bleeding in approximately 80 per cent of patients and a further session will increase the control rate to 95 per cent[1]. It has been suggested that intravenous administration of drugs such as metoclopramide, which contract the lower oesophageal sphincter and so reduce blood flow through the varices, may facilitate sclerotherapy[2]. However, it seems unlikely that such drugs will markedly improve the impressive control rate achieved by sclerotherapy alone. When two courses of injection sclerotherapy fail to control bleeding, emergency oesophageal transection usually achieves haemostasis, but the results in terms of mortality rate are far from encouraging, particularly in patients with severe liver dysfunction[3]. Therefore, it has been suggested that improvements in mortality rate will be achieved only if oesophageal transection is carried out without delay when sclerotherapy fails, since cirrhotic patients do not tolerate prolonged periods of bleeding[4]. Unlike portal–systemic shunting or oesophageal transection, the mortality and morbidity associated with injection sclerotherapy are comparatively low, even in patients with severe hepatic dysfunction. However, the facilities for 24-h endoscopy or the expertise to inject copiously bleeding varices are not always available at the admitting hospital. Therefore, in many centres there is a need for an effective immediate treatment to control bleeding until definitive therapy can be carried out. Temporary therapies for the control of bleeding can be broadly divided into two categories, namely mechanical compression of the varices by balloon tamponade, and the administration of vasoactive drugs that reduce blood flow in the varices and so promote cessation of bleeding.

Numerous reports indicate that balloon tamponade of the oesophagus is a relatively effective treatment for the control of acute variceal haemorrhage in approximately 70–90 per cent of patients. It does, however, have several serious drawbacks. First, approximately half of the patients in whom haemostasis is achieved rebleed rapidly when the balloons are deflated. Second, balloon tamponade is associated with a complication rate of about 25 per cent, even in experienced hands[5]. Serious complications such as oesophageal perforation or ulceration and aspiration pneumonia are encountered in up to 15 per cent of patients. Finally, since oesophageal tamponade is uncomfortable and unpleasant, the patient often becomes agitated, which in turn puts greater demands on the attendant nursing and junior medical staff.

Given the choice, both patient and medical staff would prefer vasoactive therapy if it were effective. Vasopressin was the first vasoactive drug introduced to control acute variceal bleeding and has been used widely for this purpose for 35 years. However, the results of numerous controlled trials and uncontrolled series indicate that this drug is effective in controlling bleeding in only about 50 per cent of patients and is associated with major complications in around 25 per cent[3]. In recent years, attempts at increasing the efficacy of vasopressin and reducing its side-effects have revolved around the use of an analogue, triglycyl-lysine-vasopressin (Glypressin;

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Ferring, Feltham, UK), or the concomitant administration of nitroglycerin. However, randomized controlled trials, comparing vasopressin or placebo with Glypressin or combination vasopressin–nitroglycerin therapy, have provided conflicting results with respect to the control of bleeding and reduction of side-effects[6].

Somatostatin lowers portal pressure in cirrhotic patients, and ten randomized controlled trials have been carried out to examine its efficacy in controlling the acute variceal bleed. Overall, the results of these trials are promising, acute bleeding being controlled in 70 per cent of patients[7]. Moreover, in no trial was any serious side-effect of somatostatin therapy observed, suggesting that the hormone is safe and efficacious. The only major drawback with the routine use of native somatostatin is its high cost compared with all other relevant treatments. An attractive alternative to somatostatin is its long-acting analogue, octreotide (Sandostatin; Sandoz, Basel, Switzerland), which is the least expensive vasoactive drug currently available for the control of acute variceal bleeding. So far, only one randomized controlled trial examining the efficacy of octreotide has been published in full. The results indicate that the drug is as effective as balloon tamponade and, as with somatostatin, there were no major side-effects[7]. However, the rate of infusion of octreotide used in that trial ($25\,\mu g\,h^{-1}$) was only half that which we have found necessary to elicit a maximal decrease in portal pressure. The preliminary results of our current trial (48 patients), comparing octreotide ($50\,\mu g\,h^{-1}$) with injection sclerotherapy, suggest that the treatments are equally effective in controlling variceal bleeding. Further trials are required to confirm the efficacy of octreotide.

In conclusion, somatostatin and octreotide appear at the moment to be the vasoactive treatments of choice for the control of the acute variceal bleed, on account of their efficacy and almost complete lack of side-effects. In addition, preliminary data indicate that after injection sclerotherapy somatostatin is effective in controlling recurrent bleeding from the varices themselves[8], oesophagitis and oesophageal ulceration[9]. Octreotide also appears to be effective in all of these situations (S.A.J. and R.S., unpublished observations). Thus if somatostatin and octreotide are shown in randomized controlled trials to be effective, not only in controlling bleeding after injection sclerotherapy but also in controlling haemorrhage before endoscopy and so facilitating injection sclerotherapy, there would be a good case for advocating the routine use of these vasoactive drugs.

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# Unilateral parathyroid exploration

Primary hyperparathyroidism is a common disease and many patients experience symptoms and demonstrate complications of their hypercalcaemia; surgical intervention in the form of cervical exploration is now being implemented with increasing frequency.

In a high proportion (80–90 per cent) of individuals the underlying pathological lesion is a solitary parathyroid adenoma. In the remaining patients multiglandular disease is present. The standard operative strategy has been bilateral neck exploration, attempted identification of all four parathyroids, and removal of obviously enlarged glands. This approach has resulted in unnecessary surgical exploration of the contralateral side of the neck in the great majority of patients whose hyperparathyroidism was caused by a solitary adenoma.

Against this background, unilateral cervical exploration for patients with a single parathyroid adenoma represents an attractive surgical option, if the side of the solitary tumour can be identified; this may occur either by chance at operation (i.e. on the first side exposed) or before surgery using ultrasonographic or scintigraphic localization techniques.

The philosophy of unilateral parathyroid exploration was first expounded by Roth and colleagues[1] and developed by Tibblin and associates[2]. Both of these groups practised blind exploration of the neck with termination of the operation if an adenoma was located on the side initially explored. Compared with patients who underwent bilateral cervical exploration, Tibblin *et al.* found that those who had a unilateral operation experienced less hypocalcaemia after surgery and had a significantly shorter mean operation time[2]. More important, no patient who underwent unilateral exploration experienced recurrent hypercalcaemia during a follow-up of between 2 and 7 years.

The availability of non-invasive localization techniques, such as ultrasonography and, particularly, thallium–technetium isotope subtraction scanning, now allows accurate lateralization of a significant proportion of solitary parathyroid adenomas before operation. In this hospital thallium–technetium scanning has been used routinely since 1983 for patients who are about to undergo neck exploration for primary hyperparathyroidism[3]. After experience with the investigation developed, and with an awareness of the very high incidence of single adenoma in this disease, a prospective study of scan-directed unilateral parathyroid exploration for those patients who had a positive scan was started. Such a surgical approach produced encouraging results in a small series of patients reported by Biller and colleagues[4] in 1986.

Since 1985 the surgical strategy, for patients coming to first-time cervical exploration for primary hyperparathyroidism and who have an isotope scan showing a single 'hot-spot', has involved a scan-directed unilateral operation with removal of the parathyroid adenoma and biopsy of the ipsilateral normal gland. Bilateral cervical exploration is performed if: (1) the isotope scan fails to demonstrate an adenoma; (2) the scan shows more than one 'hot-spot'; (3) two enlarged parathyroids are encountered on the side initially explored; or (4) familial hyperparathyroidism or multiple endocrine neoplasia is suspected. If an adenoma is not located on the side suggested by the scan, exploration of the contralateral side of the neck is, of course, carried out. This policy has resulted in a significant reduction in operating time for those patients submitted to unilateral exploration (mean 26 min) and, critically, leaves them no more vulnerable to persistent or recurrent hypercalcaemia than those undergoing standard bilateral cervical exploration[5]. It is acknowledged that the isotope subtraction scan will prove to be of positive help in guiding the surgeon to the site of the tumour in only 55–60 per cent of patients with solitary parathyroid adenoma, but this is not a reason for failing to use the scan information for those individuals in whom the investigation is positive. The logic of a scan-directed but routine bilateral cervical exploration for patients with a single parathyroid adenoma is difficult to follow[6].

The advantages of unilateral parathyroid exploration for solitary adenoma include not only a reduced operating time without jeopardizing the potential for cure, but also elimination of the risk of recurrent laryngeal nerve and parathyroid injury on the unexplored side and, possibly, a consequent reduction in the incidence of hypocalcaemia after operation. Opponents of the philosophy of unilateral exploration

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argue that such a strategy may result in a second adenoma, situated on the unexplored side of the neck, being missed. However, the incidence of double parathyroid adenoma is low[7,8] and in our own patients aged 65 years and over does not approach the rather startling figure of 9 per cent recently suggested by Thompson[9]. Even when double adenoma does occur, presumably one-third of the second adenomas are situated on the ipsilateral side of the neck and will be identified in any case at unilateral exploration. If hypercalcaemia should persist or recur after unilateral parathyroid exploration, reoperation on the contralateral side of the neck will involve dissection in a previously undisturbed surgical field. This should facilitate the procedure and reduce the risk of complications usually associated with re-exploration. To date, none of our initial series of 48 patients submitted to unilateral exploration for solitary adenoma has developed recurrent hypercalcaemia or required cervical re-exploration[5].

Other groups are now producing corroborative results in support of the concepts of unilateral parathyroid exploration[10–13], although the numbers of patients in these recently reported series are small. While careful surveillance should continue in the long term for any recurrence of hypercalcaemia, sufficient reliable evidence already exists to question seriously the conventional wisdom of bilateral cervical exploration for all patients with primary hyperparathyroidism. Unilateral parathyroid exploration, preferably directed by an accurate localization study, represents a more logical approach for hyperparathyroidism from a solitary parathyroid adenoma.

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**Br. J. Surg. 1992, Vol. 79, September, 863–866**

# Surgical treatment of hidradenitis suppurativa

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*The management of hidradenitis suppurativa is frequently unsatisfactory. No method satisfies all requirements for the ideal treatment – quick healing, no hospital admission, minimal patient inconvenience and low recurrence – but greater awareness of the strengths and weaknesses of existing methods should lead to improved management. Good reports of the relative cure rates of the different surgical options are scarce and controlled trials non-existent, but existing evidence is reviewed critically and summarized. The operation of choice in most instances is wide local excision and healing by secondary intention.*

The ideal treatment of hidradenitis suppurativa (HS) should provide a high likelihood of cure with a low recurrence rate, should avoid hospital admission and general anaesthesia, and should involve minimal inconvenience and time off work for the patient. The disease shows a wide spectrum of severity; many cases remain mild and never progress beyond one site, and some undergo spontaneous remission. However, some untreated patients can be expected to progress relentlessly until total involvement of individual and additional apocrine areas is complete[1]. Properly diagnosed and adequately treated, early stages of the disease can often be controlled with medical measures. However, in established HS there is no evidence that treatment other than surgery has any effect on the natural history of the condition. As the disease becomes more chronic, obtaining complete resolution is increasingly difficult and in advanced cases may be impossible[2].

HS is a chronic, suppurative and cicatricial disease of apocrine gland-bearing skin areas, principally the axillae, anogenital skin and, rarely, the breasts. The disease was first documented in 1839 by Velpeau[3], who reported a peculiar localization of cutaneous abscesses to the axillary, mammary and perianal skin; both Lane[4] in 1933 and Brunsting[5] in 1939 described the clinical features of the disease more fully and its frequent association with acne. Shelley and Cahn demonstrated an experimental model of the disease[6].

## Incidence

HS occurs in both sexes[7], although women develop the axillary form more frequently, while men show a greater tendency towards perianal involvement[8]. It does not often occur before puberty, and a postmenopausal onset is rare[9]. There is no racial predilection[10]. A tropical environment favours the development of HS, but it has been seen in many parts of the world under varying climatic conditions[11]. Obesity and a genetic tendency to acne are apparent predisposing factors[12,13]. Although HS is confined primarily to adults, a case has been described affecting the perineum of a 2-year-old child[11] and the disease has also been noted in a Shetland sheepdog bitch[14].

## Pathogenesis

HS appears to be a poral occlusive disease with an added element of bacterial infection. The early sequential changes include first a keratinous plugging of the apocrine duct, then dilatation of the gland, followed by severe inflammation[15]. Bacteria, which gain access to the apocrine system via the follicle, are trapped beneath the keratinous plug and multiply rapidly in the nutrient milieu of the apocrine sweat[16]. Gland rupture occurs, leading to extension of infection to adjacent apocrine glands[17]. Superadded bacterial infection with streptococci and staphylococci may lead to further local extension, tissue destruction and skin damage[18]. Fibrosis and sinus track formation result; these ultimately burn out, leaving damaged tissue that may subsequently flare up[19]. Other apocrine areas, e.g. the opposite axilla and the anogenital and mammary areolar glands, may be involved either synchronously or later[20]. Apocrine glands of the axillary skin[21] are confined mainly to the hair-bearing area and the surrounding 2 cm. The term 'anal organ' has been applied to the similarly concentrated mass of apocrine tissue situated in the circumanal region[22]. Adequate surgical excision of glands from these sites will be followed by a low recurrence rate. Apocrine glands are more diffuse in the groin, perineum and inframammary regions, making complete removal difficult; recurrence after surgery at these sites occurs more often. Recurrent disease may therefore reflect either too limited an excision or widespread, sometimes 'ectopic', gland distribution. Recurrence in the first instance usually requires further surgery to complete the excision; in the latter case it can be managed conservatively or by local removal of the recurrent lesion. This is discussed further under surgical treatment.

The exact mechanisms predisposing to these events remain unclear but may involve one of several features. HS has been simulated by producing poral occlusion and added bacterial infection. However, it is unclear whether occlusion is primary or secondary[20]. HS is associated with various physiological hormonal events, e.g. onset of puberty and pregnancy, and is also commoner during the second half of the menstrual cycle, which implies that a high oestrogen:androgen ratio may predispose[23]. The disease is also seen in association with overt endocrine disorders such as diabetes, Cushing's disease and acromegaly[24,25]. However, a recent paper examining glucose tolerance, clinical features, microbiology, immunology and human leucocyte antigen frequencies failed to show any definite pattern in 27 patients[26]. It has also been suggested that the disease may be related to reduced cutaneous levels of the protective calcium-binding protein calprotectin, and also reduced zinc and ascorbate levels[27]. A high incidence of atopy, eczema and drug allergies has also been reported[28]. There is no significant difference in the size or density of the apocrine glands in patients with HS compared with controls, but the apocrine glands in those with axillary hyperhidrosis are significantly larger than in HS or controls[21].

HS is associated with other skin diseases that show poral occlusion, e.g. Fox–Fordyce disease[29], pityriasis rubra

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pilaris[30], acanthosis nigricans[31] and steatocystoma multiplex[32]. Variable abnormalities have been described in gonadotrophin, prolactin and thyroid-stimulating hormone levels[7]. HS has previously been shown to be associated with hyperandrogenaemia and to respond to antiandrogen therapy[33]. It has been suggested that, as most subjects with HS have normal androgen levels, this disorder is more likely to result from an enhanced end-organ response than to increased androgen production. However, when the activities of three peripheral androgen-converting enzymes were measured in axillary apocrine glands from controls and patients with HS, it was found they did not differ significantly. Hence, HS cannot be attributed to raised activities of end-organ androgen-converting enzymes[33].

## Complications

Folliculitis and other local or systemic infections resulting from the spread of bacteria, marked fibrosis of an infected area with restricted mobility of the associated limb, anal and rectal fistulation in the perianal form of the disease and, rarely, squamous cell carcinoma of the skin may all occur[34]. Other complications that have been reported include urethral, vesical and rectal fistulae[35], anaemia[36], interstitial keratitis[37], hypoproteinaemia, and amyloidosis, which may rarely progress to renal failure and death[38].

## Medical management

Initial treatment comprises cleaning with ordinary soaps, careful drying, povidone–iodine (Betadine; Napp Laboratories, Cambridge, UK) and other antiseptics. Open, wet dressings and loose clothing are indicated[39]. Mild topical steroid creams are of use, but are often more effective in combination with systemic antibiotics such as penicillin, erythromycin or tetracycline[40,41]. This produces clearance of mild attacks in about one-third of cases and can also stop initial disease progression. Topical antibiotics of the aminoglycoside group, e.g. clindamycin, can also reduce cutaneous inflammation[41]. Intralesional triamcinolone may produce regression[2]. Control of HS has also been reported in mild to moderate cases in women using combined antiandrogen (cyproterone acetate) and oestrogen therapy[42]. A separate double-blind controlled, cross-over trial comparing ethinyloestradiol 50 μg plus cyproterone acetate 50 mg in a reverse sequential regimen with ethinyloestradiol 50 μg plus norgestrel 500 μg showed that these treatments were equally effective[43], although only seven of 18 patients who completed the trial were free of disease at 18 months' follow-up. Patients with established sepsis secondary to extensive hidradenitis responded less well, reinforcing the need for early diagnosis and treatment if conservative measures are to offer any chance of success.

Synthetic retinoids (acitretin) have also been successfully employed in clearing hidradenitis when applied topically, but experience is limited[44,45] and one trial failed to confirm any advantage[46]. Combination hypothalamic–pituitary–ovarian axis and adrenal suppression has also been used with some benefit[47]. Earlier studies failed to show any improvement from stimulating the hypothalamoadrenal axis with polysaccharides derived from bacteria, and even insulin and thyroxine administration have been tried unsuccessfully[48].

## Surgical treatment

Operative treatment must be performed in conjunction with medical management. Incision and drainage of individual lesions may lead to temporary control of symptoms but is best avoided since there is underlying sepsis, and abscesses almost inevitably recur[49]. Once infection has been treated with antibiotics, tracks may be carefully excised[49]. Exteriorization and diathermy of lesions is an alternative technique with comparable results[50]; complete excision of axillary and perineal skin is often needed to prevent recurrence.

As an aid to obtaining complete clearance, it may be possible to visualize the apocrine glands completely by staining with 2 per cent iodine–starch in alcohol (75 mg in 100 ml castor oil), blocking exocrine sweating with atropine (1·2 mg intravenously), and stimulating apocrine glands with oxytocin (2 units intravenously). The resulting gap in skin cover may be left to heal primarily by granulation[51]. Silastic (Dow Corning, Reading, UK) foam may be a useful adjunct to this process. Of 17 patients undergoing radical excision of HS whose wounds were allowed to heal by granulation, axillary excisions were performed in nine and perineal surgery in the remainder. Initially the cavity was packed with ribbon gauze soaked in a proflavine–liquid paraffin mixture. On the third day after operation Silastic foam dressing was applied. Axillary excisions required 50 ml and perineal excisions 100–200 ml Silastic mixture. Proponents of this technique claim that it permits adequate disease clearance and results in a cosmetically acceptable scar, superior to that obtained by skin grafting and with little limitation of movement. It also avoids the pain of conventional management of open granulating wounds by gauze packing[51].

Once the defect is bacteriologically clean, various methods may be used to facilitate healing (*Table 1*). Skin grafts have been employed, the thigh being a common donor site. Rotational flaps and free flaps have also been used by plastic surgeons[51–62]. However, the terms 'wide' and 'radical' excision are poorly defined in many papers, and so general comparison of the various methods is unsatisfactory. Emphasis is often placed on the technique used to cover an excision defect, rather than on the extent of excision or the success or failure of the treatment. Follow-up has been short[63] or of unspecified length[64] and often absent[65,66]. Recurrence rates that are quoted without reference to the site at which surgery was performed may mislead[63], and considering reoperation as a criterion of treatment failure will underestimate the number of patients with a less than satisfactory outcome[16]. *Table 1* gives a summary of all series published in sufficient detail to allow meaningful comparison, although some data are either unavailable or unclear. Harrison *et al.*[62], in the most complete survey available, reviewed 82 patients who had been treated by radical surgery (118 excisions) from 6 to 89 months after surgery. Local recurrence rates varied greatly with the disease site, being low after axillary (5 per cent) and perianal (nil) surgery and high after inguinoperineal (37 per cent) and submammary (50 per cent) excision. Recurrence resulted mainly from inadequate excision or an unusually wide distribution of apocrine glands, but physical factors such as obesity, local pressure and skin maceration also played a part in a few patients. Recurrence resulting from inadequate surgery tended to be the most troublesome and 25 per cent of patients developed disease at a new anatomical site after operation. Two distinct patterns of recurrent disease were found. One was confined to the immediate vicinity of the scar, usually solitary and typically occurring in the groin creases or the posteroinferior margins after inguinoperineal surgery. The second, in which multiple lesions were present, occurred either adjacent to previous excision sites or a few centimetres away. The former, typified by deep sinuses and appreciable morbidity, required further excision; the latter, characterized by widespread, often superficial lesions, was trivial and resulted in little morbidity[62]. In this series, all complications were relatively minor. Failure of the skin graft, defined as < 50 per cent take, occurred in nine patients (45 per cent of applied grafts) despite delayed application and adequate immobilization. Two patients had hypertrophic scars and one had wound tenderness[62]. Significantly, 91 per cent of patients were pleased with the results of surgery at follow-up. The extent of skin excision may influence recurrence more than the method of wound management[67]. In another series, reoperation for axillary recurrence was necessary in 54 per cent of patients treated by local excision and primary suture, in 19 per cent after flap repair, and in 13 per cent after grafting[16]. This implies that attempts to obtain primary skin cover may lead to inadvertent compromise of the excision margin and an increased risk of recurrence.

**Table 1** *Options for surgical treatment of hidradenitis suppurativa*

| Method | No. of procedures | Hospital stay after operation (days) | Time to healing (weeks) | Recurrence |
|---|---|---|---|---|
| Excision of axillary and perineal skin; Silastic foam[51] | 17 | 5–30 (mean 15) | Mean 8 (range 6–14) | 1 at 1 year (perineal) |
| Primary closure[52,53] | 24 (Reference 53) | 7–20 | 6–12 | 11 followed up 1 year or more with 1 recurrence at 2 years |
| Split skin graft[55,56] | 41 | 7–14 | 6–8 | 6 at 1 year |
| Skin graft and stapling[57] | 30 | 7 after graft (but grafts multiple and staged) | 4 | 2 at 1 year |
| Staged resection and skin grafting[57] | 35 | 28–42 (staged) | 4–6 | 5 at 1 year |
| Flap grafts[58,59] | 27 | 16–30 | 5–8 | 3 at 1 year |
| Pedicle grafts[60] | 18 | 14 | 4–8 | 3 at 1 year (data unclear) |
| Excision and skin graft[54] (superficial axilla) | 23 | 7–14 | 6–8 | 0 at 2 years |
| Excision and skin graft[54] (deep axilla) | 9 | 14–21 | 6–8 | 2 at 2 years |
| Excision and skin graft[61] (perineum) | 38 | 21 | 6–8 | 29 at 8 years (45% needing further operation) |
| Excision and Silastic foam[62] | | | | |
| Axillary | 56 | n.a. | Mean 11 (range 7–30) | 3 at 6 years |
| Perineal | 15 | | n.a. | 0 at 6 years |
| Inguinoperineal | 41 | | Mean 16 (range 8–30) | 15 at 6 years |
| Mammary | 6 | | Mean 17·5 (range 12–30) | 3 at 6 years |

Data for some treatments are composites of several series from different papers. n.a., Not available

Other more aggressive surgical options include orchidectomy in patients with severe perineoscrotal involvement[49]; the use of a preliminary diverting colostomy to aid healing in this form of HS has also been recommended[68]. Radiotherapy has been used in some series but often fails to eradicate the lesion completely; troublesome sinuses and scarring may follow[69].

## Conclusions

HS is a complex disease, the rational treatment of which depends on a consideration of the pathogenetic mechanisms involved[70–73]. Although the acute, intermittent lesions of early HS often respond to antibiotics, it is unlikely that treatment alters the clinical course of the disease. Patients with chronic disease may occasionally derive symptomatic benefit from a long-term course of antibiotics, but relapse is almost inevitable when such treatment is withdrawn. If other medical measures, e.g. endocrine therapy, are to be used, early diagnosis is essential: late disease with sepsis can be successfully treated only by operation. Comparative assessment of the various surgical approaches is difficult because of incomplete reporting of results and lack of any controlled trial data. An attempt has been made to rationalize the available information in this review and hence clarify 'best practice'. It appears that radical excision and controlled healing with Silastic foam gives good symptomatic control of severe HS of the axillary, inguinoperineal and perianal regions, but is less satisfactory for the rare submammary disease. Skin grafting and flaps should be reserved for severe recurrent disease not responding to simpler measures and affected patients should be referred to a specialist unit.

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# Paediatric intussusception

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*Intussusception is one of the commonest causes of intestinal obstruction in infants and accounts for about 700 hospital admissions each year in England and Wales. Improved results of treatment have followed recent technological developments, which include ultrasonographic imaging and pneumatic reduction techniques. Most intussusceptions can be reduced successfully without the need for operation but close cooperation between surgeon and radiologist is essential. Mortality and morbidity rates from the condition have progressively declined in recent decades but avoidable deaths still occur.*

Intussusception, the invagination of one portion of the intestine into an adjacent segment, occurs infrequently yet is one of the commonest abdominal emergencies in paediatric surgery. The condition has been recognized for hundreds of years but was first accurately described by John Hunter[1] in 1793 (*Figure 1*). During the 19th century, reduction by means of hydrostatic enemas, rectal insufflation of air or gas, or manipulation with a wand were all attempted[2]. The first successful operative reduction was performed by Jonathan Hutchinson[3,4] in 1871.

In 1876, Hirschsprung published the first of several papers on the reduction of intussusception by hydrostatic pressure[5], and in 1926 Hipsley reported a series of 100 patients treated with this technique[6]. One year later, several authors[7–10] independently described the use of radiologically controlled contrast enema reduction, which became the definitive non-operative method of management after its popularization by Ravitch and McCune[2,11] in 1948.

## Incidence and epidemiology

Many of the epidemiological studies of intussusception were performed more than 30 years ago when its incidence varied from 1·5 to 4·3 per 1000 live births[12–15]. Recent data suggest that the figure may be higher in China[16] but is about 2·4 per 1000 live births in Sweden and New York[17,18]. In Scotland the incidence may be declining[19] but in England and Wales[20] hospital admissions remain at about 700 per year. Annual fluctuations may reflect environmental influences such as viral epidemics[21]. In temperate climes, a seasonal incidence has been reported with a peak in summer[17,22–24] but this has not been an invariable finding[2,12]. In Nigeria there is a greater proportion of older children with caecocolic intussusception and subacute or chronic presentations[25,26], and in southern Africa colocolic sigmoid intussusception is peculiarly common[27].

The condition can present at any age but only 10–25 per cent of cases occur after the age of 2 years, the peak incidence being between the fifth and ninth months of life. It may occur in the neonatal period[28,29] and even prenatally as a rare cause of intestinal atresia[30,31]. Overall, 60–70 per cent of intussusceptions arise in males[2,12,22,32], with a greater proportion of boys in older age groups[12]. Affected infants are no better nourished than normal[17] and up to 16 per cent may be malnourished[33].

## Pathology

Intussusception results in compression and angulation of the mesenteric vessels of the invaginated bowel, leading to a strangulating obstruction. Necrosis begins in the outer layer of the intussusceptum at its apex and extends proximally[34]. The intussuscipiens may suffer from secondary ischaemic pressure necrosis resulting in free perforation or prolapse of the intussusceptum into the peritoneal cavity[35]. In animal studies, pathogenic bacterial translocation to the serosal surface of the bowel rapidly occurs even with viable intussusceptions[2].

The condition has been classified according to the site of the inner intussusceptum and outer intussuscipiens. More than 80 per cent involve the ileocaecal region, with the isolated ileoileal, caecocolic, colocolic and jejunojejunal varieties being progressively rarer. Ileocolic intussusception usually starts several centimetres proximal to the ileocaecal valve as a short ileoileal invagination which then advances into the colon, but some have a long ileoileal component. Approximately 80 per cent of ileocolic intussusceptions have their apex in the ascending or transverse colon[2].

Multiple small bowel intussusceptions, either antegrade or retrograde, have been observed at autopsy (agonal intussusception) and are thought to be caused by small bowel dysmotility around the time of death. Similar multiple, short-segment invaginations have occurred either spontaneously[36] or in survivors of abdominal trauma[37]. Isolated retrograde small bowel intussusception has been described[38] and both gastroduodenal and duodenogastric invaginations have been reported as complications of gastrostomy tubes[39,40].

There is abundant evidence that some acute episodes resolve spontaneously, either by reduction or by sloughing and passage

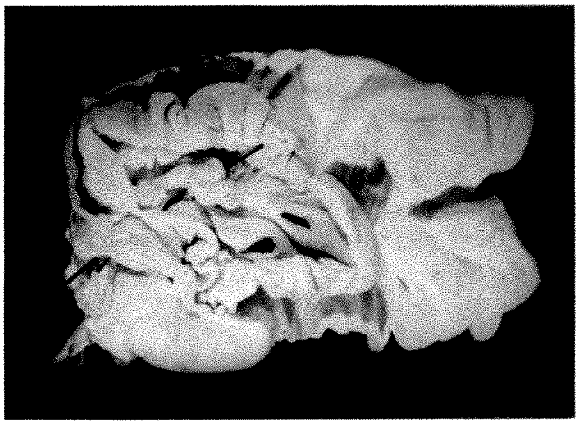

**Figure 1** *John Hunter's specimen of an ileocolic intussusception from a 9-month-old boy. The invaginated terminal ileum and appendix have been fenestrated. Reproduced by kind permission of the President and Council of The Royal College of Surgeons of England*

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**Table 1** *Pathological lead points in intussusception*

- Structural
  - Meckel's diverticulum[69–72]
  - Ectopic gastric mucosa[73,74]
  - Ectopic pancreas[48]
  - Appendix (normal, appendicitis or mucocele) or appendiceal stump[43,61,75,76]
  - Enteric duplication cyst[2,77,78]
  - Anastomotic suture line[70,79]
- Vascular/haematological
  - Henoch–Schönlein purpura[80]
  - Haemophilia[22,81]
  - Abdominal trauma[82]
  - Leukaemia[83,84]
  - Idiopathic thrombocytopenic purpura[85]
  - Haemolytic–uraemic syndrome
- Neoplastic
  - Polyps (adenomas, hamartomas (Peutz–Jeghers, juvenile), inflammatory fibroid polyp, lymphoid)[17,71,72,86–88]
  - Small bowel carcinoid tumours[71,89]
  - Haemangioma[72,89,90]
  - Lymphangioma[91]
  - Lipoma[92]
  - Adenomyoma[93], mesenchymoma
  - Leiomyoma[94]
  - Lymphoma/lymphosarcoma*[95,96]
  - Fibrosarcoma[72]
  - Metastatic tumours[84]
  - Colonic adenocarcinoma[97]
- Inflammatory
  - Foreign bodies, e.g. trichobezoars[98,99]
  - Granulomas (amoebic, eosinophilic, Crohn's)[100,101]
  - *Ascaris lumbricoides*[89,102]
  - Cystic fibrosis*[103]

*Particularly subacute or chronic intussusception in older children

of the gangrenous intussusceptum with union of the bowel at the neck of the intussusception[41–46]. Short, transient invaginations are occasionally found during laparotomy for other conditions and sometimes there is a past history of a suspected, spontaneously resolving episode in a patient with proven intussusception[2].

## Aetiology

### *Primary idiopathic intussusception*

The wall of the terminal ileum of infants is rich in lymphoid tissue and in approximately 90 per cent of cases there is no obvious cause other than hyperplasia of this lymphoid tissue[47]. An upper respiratory tract infection or enteritis commonly precedes development of the condition[2,48]. Adenoviruses, and to a much lesser extent the rotavirus, have been implicated in up to 50 per cent of cases[49–53]. Because many infants are immunized during the period of peak incidence of intussusception the two events may coincide, but there is no discernible relationship with polio virus immunization (M.D.S., unpublished observations). Other potential factors of aetiological importance include changes in the diet of the weaning infant, loss of passively acquired maternal immunity and the disproportionate diameters of the infant's ileum and caecum; there are no hard data on these aspects.

Lymphoid hyperplasia may be responsible for the lead point in idiopathic intussusception, but does not explain why some infants develop the condition and others do not despite exposure to similar environmental influences. The condition has not been regarded as having any hereditary basis[2] but large series have demonstrated that 1–3 per cent of children have affected siblings[12,54]. This could be explained by common exposure to an environmental precipitant such as a virus[55] but this mechanism does not account for the occurrence of the condition in sequential generations[56,57]. In some families the incidence of recurrent intussusception raises the possibility of inherited predisposing anatomical anomalies such as malfixation of the ileocaecal mesentery.

An unfixed caecum, attached to the posterior abdominal wall by way of a mesentery, is found at autopsy in 20 per cent of infants[58] and a high mobile caecum with failure of complete intestinal rotation has been implicated in the pathogenesis of intussusception[25,59–62]. Intussusception accompanied by malrotation, with or without mid-gut volvulus, has been described by several authors[17,59,63–67]. By way of its association with malrotation, the condition has a link with duodenal stenosis, which may explain why some affected infants have failed to thrive[68]. The incidence and significance of mid-gut malrotation and its relationship to intussusception deserve further investigation, but mid-gut volvulus does not appear to have been reported as a late complication of non-operative reduction.

### *Secondary intussusception*

In 2–12 per cent of patients the condition is secondary to a distinct pathological lead point or underlying abnormality (*Table 1*)[17,21,23,43,48,69–104]. With the exception of neonates, secondary intussusception is progressively more likely with advancing age and in those with recurrent intussusception. After the age of 2 years, a pathological lead point is found in one-third of patients[72] and in one-half of those with a recurrent condition[32], whereas under the age of 2 years secondary intussusception occurs in less than 4 per cent[72,105].

Both Meckel's diverticulum and duplication cysts can cause intussusception throughout childhood; the former is the commonest pathological lead point. Intestinal polyps and lymphomas affect older children[71,72,96]. Small bowel tumours are rare in children but most often present with intussusception[71]. Over the age of 3 years, ileal lymphoma or lymphosarcoma should be considered in all patients, especially in those with chronic ill health or an irreducible intussusception[95,96]. To our knowledge, the condition has not yet been reported in association with small bowel tumours or atypical infections in children with the acquired immune deficiency syndrome. Subacute presentation of ileocolic intussusception occurs in about 1 per cent of 9–12-year-old children with cystic fibrosis and is thought to be precipitated by abnormally viscid bowel contents[103,106].

Postoperative intussusception affects both sexes equally but accounts for only 1–2 per cent of all cases[17,22,107]. These are commonly ileoileal invaginations and 90 per cent are confined to the small bowel; this form has occurred after a wide range of procedures (*Table 2*)[76,107,108]. The operation need not directly disturb the abdominal contents, e.g. cervical lymph node biopsy[109], ventriculoatrial shunt revision[110], inguinal herniotomy or thoracic surgery[79].

**Table 2** *Surgical procedures preceding postoperative intussusception in 178 patients*[17,76,79,107,108]

| Procedure | No. of patients |
|---|---|
| Abdominoperineal pull-through procedures | |
| Hirschsprung's disease | 15 |
| Anorectal anomalies | 7 |
| Appendicectomy | 17 |
| Reduction of ileocolic intussusception* | 16 |
| Meckel's diverticulectomy | 9 |
| Nissen fundoplication | 16 |
| Wilms' tumour excision | 13 |
| Neuroblastoma excision | 14 |
| Urinary tract surgery | |
| Coloureterostomy or ileal conduit | 4 |
| Cutaneous ureterostomy | 3 |
| Open bladder biopsy | 1 |
| Bladder augmentation | 1 |
| Miscellaneous abdominal and extra-abdominal operations | 62 |

*Excludes recurrence of ileocolic intussusception

**Table 3** *Frequency of classical symptoms and signs in recent studies of intussusception*

| Reference | Year | Place | No. of patients | Abdominal pain (%) | Vomiting (%) | Rectal bleeding* (%) | Symptom triad (%) | Abdominal mass (%) |
|---|---|---|---|---|---|---|---|---|
| Hutchison *et al.*[42] | 1980 | Glasgow | 209 | 82 | 80 | 46 | — | 50 |
| Pollet[104] | 1980 | Aberdeen | 77 | 89 | 97 | 45 | 38 | 56 |
| Raudkivi and Smith[112] | 1981 | New Zealand | 98 | 49 | 81 | 63 | 20 | 61 |
| Man *et al.*[113] | 1983 | South-east England | 75 | 87 | 84 | 61 | 46 | 70 |
| Sparnon *et al.*[23] | 1984 | Australia | 128 | 81 | 74 | 56 | 45 | 56 |
| Liu *et al.*[67] | 1986 | Dublin | 66 | 89 | 89 | 50 | — | 74 |
| Beasley *et al.*[32] | 1987 | Australia | 580 | 84 | 91 | 63 | — | 79 |
| Bruce *et al.*[17] | 1987 | USA | 583 | 85 | 68 | 37 | 21 | 48 |
| Mackay *et al.*[24] | 1987 | Australia | 91 | 93 | 95 | 46 | — | 77 |
| Winstanley *et al.*[114] | 1987 | Manchester | 78 | 83 | 89 | 65 | 20 | 60 |
| Wilson-Storey *et al.*[61] | 1988 | Edinburgh | 125 | 88 | 86 | 56 | > 50 | 63 |
| Mean | | | | 83 | 85 | 53 | 32 | 63 |

*Overt rectal bleeding or noted on rectal examination

That intussusception after operation is almost always limited to the small bowel, and that it most often follows certain types of operation, suggests that its pathogenesis is different from that of the commoner idiopathic form. A neurogenic mechanism producing intestinal dysmotility is the most likely cause and anaesthetic agents may also be important. Small bowel intussusception has been reported after the administration of vincristine, which is known to cause intestinal dysmotility[84], and after faradic stimulation of the bowel or premotor cortex of experimental animals[2,111].

## Clinical features

### *Acute ileocolic intussusception*

Classically, intussusception is said to present in a previously healthy baby who develops repeated screaming attacks accompanied by pallor and drawing up of the legs. Between episodes the infant initially appears well but later becomes restless and refuses feeds. Vomiting follows and becomes bilious. A normal stool may be passed followed by blood from the anus, either in the form of pink mucus or 'redcurrant jelly'. Progressive dehydration and strangulating intestinal obstruction are usually fatal within 5 days.

The frequency of classical signs and symptoms is age and site related (*Table 3*)[112–114]. Vomiting is the commonest feature and may be the sole presenting sign in infants, while older children tend to complain of colicky abdominal pain. Constipation may be a late feature. The intussusception prolapses through the anus in 1–2 per cent of patients[17,42,48].

The typical lesion is palpable as a tender 'sausage' in the right hypochondrium or epigastrium but a mass may be discovered at any site along the line of the colon[48,61]. The detection of a mass depends on the skill of the clinician and the degree of abdominal relaxation or distension in the infant. Rectal examination often reveals blood and rarely the apex of an intussusceptum. Late signs include abdominal distension, hypovolaemic shock and peritonism. Fever is common and hyperpyrexia indicates a poor prognosis[2,20].

Atypical presentation results in delayed diagnosis and treatment[115]. Diarrhoea occurs in 7–30 per cent of patients[17,23,24,42,48,114,115] and the erroneous diagnosis of gastroenteritis may lead to a fatal delay in treatment[2,20,115]. The apparently 'painless intussusception' occurs in 13–20 per cent of patients[23,42,116], who take twice as long to be admitted and have a greater incidence of irreducibility than those with obvious colic[116]. Some infants present with profound listlessness and apathy prompting unnecessary neurological investigations[117,118]; endogenous opiate release has been suggested as a cause[119].

### *Acute small bowel intussusception*

Intussusceptions confined to the small bowel account for fewer than 10 per cent of paediatric cases[17,22,120]. Presentation is usually with vomiting and pain, and rectal bleeding or a palpable mass is rare. Contrast studies are often unrewarding[76,107] and the diagnosis is frequently delayed until laparotomy for intestinal obstruction is undertaken[121].

There are three situations in which small bowel intussusceptions are over-represented: in the child aged over 2 years[105,122]; in those with a pathological lead point[72]; and in the postoperative period. Two-thirds of intussusceptions following operation develop within 1 week of surgery[76,107].

### *Chronic intussusception*

Occasionally, intussusception presents in the older child with a history lasting 2 weeks or more, when the condition is non-strangulating and incompletely obstructing[123–125]. Various sites have been recorded, most commonly ileocolic. Typically there is intermittent abdominal pain, anorexia, vomiting and weight loss, with altered bowel habit, particularly diarrhoea[105,124,125]. Rectal bleeding is rare but an abdominal mass may be intermittently palpable. Malabsorption and protein-losing enteropathy may be the dominant features[124,126]. Ultrasonography or contrast studies usually establish the diagnosis.

Although uncommon, chronic intussusception may occur in cystic fibrosis[103] or with intestinal lymphoma[95,96] (*Table 1*). Hydrostatic reduction is rarely successful and operation is usually required.

## Diagnosis

A combination of clinical, ultrasonographic, radiological and operative techniques may be necessary for complete diagnosis. Plain radiography commonly shows a paucity of gas in the right iliac fossa with the intussusception visible as a soft tissue opacity in up to 50 per cent of patients (*Figure 2*). Small bowel obstruction is a late sign.

Recently, ultrasonography has emerged as a sensitive and specific diagnostic tool in the condition. On longitudinal section the mass has a tubular appearance[127–129] and in the transverse plane there is a typical target or 'doughnut' with a transonic peripheral rim, corresponding to the oedematous wall of the intussusceptum, surrounding the echogenic central area which represents its lumen (*Figure 3*). The thickness of the transonic rim may help to predict the chances of success with non-operative reduction[128,129]. The experience of the authors accords with that of Pracros *et al.*[130] who found neither false

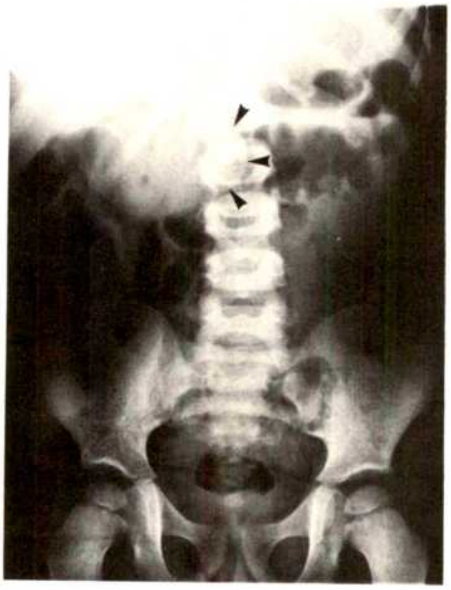

**Figure 2** *Plain abdominal radiograph demonstrating the soft tissue mass (arrowed) of an ileocolic intussusception*

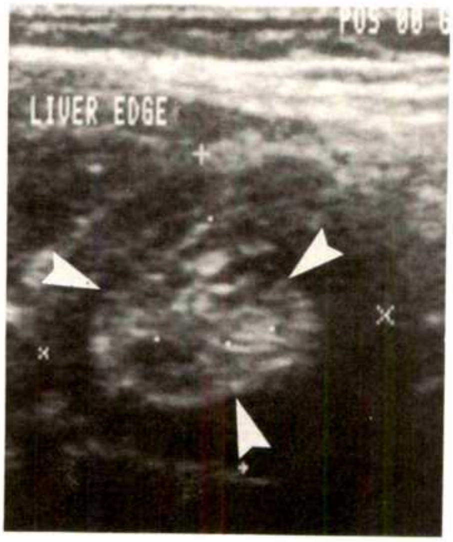

**Figure 3** *Typical ultrasonographic appearance of an ileocolic intussusception demonstrating the target sign. The transonic peripheral rim of the intussusceptum is surrounded by crosses and the echogenic central lumen indicated by arrows*

positives nor negatives, although some authors have reported the occasional false-positive result[127,128]. The experience of the ultrasonographer is important and if the diagnosis remains uncertain a contrast study must be performed.

Important benefits of ultrasonography include the ability to detect pathological lead points such as Meckel's diverticulum[131], small bowel lymphoma[127] and enteric duplication cysts[78,132], which must be distinguished from fluid trapped within the invagination[133]. Enlarged mesenteric lymph nodes and free peritoneal fluid are often discovered by ultrasonography and in some patients it is possible to identify the lymphoid hyperplasia of an apparently idiopathic presentation[78]. An expert ultrasonographer may readily diagnose intussusceptions confined to the small bowel, which is a great advance because these are often impossible to detect clinically or by conventional radiology. This is of particular value in patients who have had operations and in those with Henoch–Schönlein purpura or other haematological problems, since it may obviate the need for unnecessary laparotomy in a group of particularly sick children in whom diagnosis is always difficult[44,127,134,135].

Colonoscopy and computed tomography have been used to diagnose intussusception[136,137] but the combination of ultrasonography and conventional radiology is simpler and safer in paediatric practice.

## Treatment

Successful management of intussusception depends upon early diagnosis, resuscitation and prompt reduction. Inadequate fluid replacement is a major factor in 20 per cent of deaths[20]. The current preference of the authors is to use a colloid, such as 4·5 per cent human albumin solution, beginning with a bolus of 20 ml/kg in the hypovolaemic child, together with blood if necessary, and crystalloids for maintenance of blood glucose and serum electrolyte concentrations. Nasogastric aspiration and appropriate broad-spectrum antibiotics must be used, and continued in the patient undergoing operation to avoid deaths from aspiration pneumonitis and septicaemia[20].

### *Non-operative reduction*

It is now generally accepted that non-operative reduction should be attempted in most patients with acute idiopathic intussusception[48]. Radiological reduction techniques have been criticized for their high recurrence rates, potential to overlook pathological lead points, rare perforations, incomplete success, and radiation exposure, but these risks are more than offset by the morbidity and mortality surrounding operative reduction with its longer and more expensive recovery period[17,67,113,120]. Both hydrostatic and pneumatic reduction methods are available with monitoring by fluoroscopy or ultrasonography. There is a wide variation in the application and methodology of these techniques and their results (*Tables 4* and *5*)[138–147].

Non-operative reduction should not be attempted in units where paediatric surgical facilities are unavailable and ideally the surgeon should be in attendance to monitor the infant's condition. Resuscitation should be continued during reduction; effective sedation and analgesia improve the chances of success[148]. The authors use intramuscular pethidine compound (0·06–0·08 ml/kg) but others have recommended intravenous diazepam (250–300 $\mu$g/kg)[67], papaveretum (0·2 mg/kg)[139,149] or general anaesthesia[143,144,150]. Abdominal manipulation, antispasmodics and glucagon are of dubious value[151] but thermal environmental control is important. Some authors recommend a Foley balloon catheter[48,149] but we advocate a soft rubber rectal tube held in place by firm buttock strapping. Traditional practice dictates a barium column of 1 m for a maximum of 10 min if the intussusception is static[48], but efforts at radiological reduction should be tailored to the condition of the patient and the progress of the reduction. Steady progress should encourage persistent pressure in the stable infant. Radiographic screening times should be kept to a minimum. Reduction is deemed to be satisfactory only if there is free reflux of barium into the small bowel without a residual filling defect, *together with resolution of symptoms and signs in the patient.*

Absolute contraindications to non-operative reduction are signs of peritonitis or perforation, demonstration of a pathological lead point, and the presence of profound shock (although the last group of infants can undergo successful reduction after appropriate resuscitation[2,67] despite a greater risk of iatrogenic colonic perforation[152]). Perforation of the colon during hydrostatic reduction is a rare event, occurring in up to 3 per cent of attempted reductions (*Table 4*), but if promptly recognized and treated is often followed by complete recovery[89,142,152–154]. Perforations during hydrostatic reduction have occurred in ischaemic areas of the colonic intussuscipiens or in necrotic areas in the outer wall of the reducing intussusceptum[152,153].

Relative contraindications to hydrostatic reduction include chronic and neonatal intussusceptions, when the history is in excess of 48 h[67,89,155,156], if there is evidence of

**Table 4** *Recent results of hydrostatic reduction of intussusception*

| Reference | Year | Place | No. of patients | Attempted reductions* (%) | Successful reductions† (%) | Perforations‡ (%) | Recurrences§ (%) |
|---|---|---|---|---|---|---|---|
| Hutchison *et al.*[42] | 1980 | Glasgow | 209 | 27 | 58 | 0 | — |
| Man *et al.*[113] | 1983 | South-east England | 75 | 44 | 18 | 0 | 0 |
| Sparnon *et al.*[23] | 1984 | Australia | 128 | 75 | 50 | 0 | 17 |
| Liu *et al.*[67] | 1986 | Dublin | 66 | 90 | 75 | 0 | 10 |
| Mackay *et al.*[24] | 1987 | Australia | 91 | 99 | 78 | 1·1 | 17 |
| Winstanley *et al.*[114] | 1987 | Manchester | 78 | 69 | 50 | 0 | 8 |
| Zamir *et al.*[138] | 1987 | Israel | 61 | 95 | 50 | 0 | — |
| Paes *et al.*[139] | 1988 | Southampton | 89 | 80 | 42 | 1·4 | 17 |
| Phelan *et al.*[140] | 1988 | Australia | 602 | 60 | 53 | 0 | 14 |
| Wilson-Storey *et al.*[61] | 1988 | Edinburgh | 125 | 61 | 38 | 1·3 | 10 |
| Skipper *et al.*[141] | 1990 | USA | 157 | 89 | 66 | 0·7 | 21 |
| Palder *et al.*[142] | 1991 | Canada | 100 | 100 | 75 | 3·0 | 10 |

*Attempted reductions: percentage of patients in whom hydrostatic reduction was attempted. †Successful reductions: percentage of successful reductions in those patients undergoing attempted reduction (excludes recurrent intussusceptions and those in whom intussusception was found reduced at laparotomy after an initially failed reduction). The optimum figure is not 100 per cent since gangrenous bowel and pathological lead points should not be reduced. ‡Perforations: percentage of patients undergoing attempted reduction in whom perforation occurred. §Recurrences: percentage of patients undergoing successful reduction in whom there was a recurrence

**Table 5** *Recent results of pneumatic reduction of intussusception*

| Reference | Year | Place | No. of patients | Attempted reductions (%) | Successful reductions (%) | Perforations (%) | Recurrences (%) |
|---|---|---|---|---|---|---|---|
| Guo *et al.*[16] | 1986 | China | 6396 | — | 94 | 0·1 | — |
| Jinzhe *et al.*[143] | 1986 | China | 2496 | — | 91 | 0·1 | — |
| Tamanaha *et al.*[144] | 1987 | Japan | 222 | 93 | 81 | 0 | 7 |
| Stringer and Ein[62] | 1990 | Canada | 152 | >95 | 80 | 1·1 | 8 |
| Todani *et al.*[145] | 1990 | Japan | 137 | 93 | 91 | 0 | 9 |
| Glover *et al.*[146] | 1991 | Australia | 226 | 88 | 75 | 0·5 | 7* |
| Shiels *et al.*[147] | 1991 | USA | 75 | 100 | 87 | 0 | — |
| Pablot and Stringer (unpublished data) | 1991 | South-east England | 46 | 87 | 75 | 2·4 | 5 |

See footnote to *Table 4*. *Estimate from Phelan *et al.*[140]

small bowel obstruction on plain radiography[67,153,156,157], and in children older than 2 years[29,152,155,158]. In isolation, none of these features is an absolute contraindication to attempted reduction but, in combination, the chances of success are considerably reduced and the incidence of complications significantly increased[152,155].

Most authors have found little correlation between the length of the invagination and the success of its reduction[18,120,159], although the latter is less likely once the apex has reached the rectosigmoid region[159]. Infants under 3 months of age are reported as having a reduced rate of reduction and a higher complication rate[155,158], but this is not a universal finding[156]. In neonates the relatively high frequency of pathological lead points[29] and irreducibility[160], together with diagnostic difficulties such as confusion with necrotizing enterocolitis[161], indicate a low threshold for laparotomy.

Success rates with hydrostatic reduction[18] have varied from 20 to 80 per cent (*Table 4*) and reflect local referral patterns, selection criteria, and the skill and determination of the radiologist. Gangrenous intussusceptions and those confined to the small bowel or with a pathological lead point are unlikely to be reduced[43,70–72,142,154,162,163] but some of the ileoileocolic form can be reduced, albeit with difficulty[142,152]. Successful hydrostatic reduction does not exclude a lead point[157]. The radiographs of older children must be carefully examined after reduction to exclude a filling defect, especially in the terminal ileum[163]. Ultrasonographic findings are of particular help in identifying the rare instances of a reduced pathological lead point.

Following the publication of several enormous series from China[16,143], there has been renewed interest in the technique of pneumatic reduction, a procedure successfully employed in the 19th century[2,164] and reintroduced in combination with manometric and fluoroscopic control[165] in 1959. This provides a cleaner, cheaper and more rapid method of reduction involving less distress and exposure of the patient to radiation[62,146]. As yet there are no controlled trials comparing the relative merits of air, carbon dioxide or oxygen in pneumatic reduction. With this technique, the chosen gas is carefully pumped into the rectum up to a pressure of 80 mmHg. With experience, the pressure may be increased to a maximum[62,146,147] of 120 mmHg. A low gas flow and pressure should be used at first because at higher rates some intussusceptions are reduced within seconds. The procedure is monitored by fluoroscopic control (*Figure 4*) and most invaginations[143] are reduced within 5 min.

Colonic perforation is rare[16,146] (*Table 5*) but in this circumstance free intraperitoneal air is said to be less hazardous than barium[62,147]. None the less, a pressure release device and a wide-bore needle must be available to deal with tension pneumoperitoneum. As with hydrostatic reduction, pathological lead points and ischaemic bowel are generally irreducible although there is one reported instance of a late ischaemic ileal stricture[146]. Studies employing historical controls have indicated that pneumatic techniques are more effective than hydrostatic methods of reduction, possibly because gas more readily decreases the frictional forces between the intussusceptum and the intussuscipiens[62,140,146].

Pitfalls in treatment by barium or gas enemas have been described, relating mostly to the uncertainty of complete reduction because of overlapping loops of barium-laden colon[48], difficulty in distinguishing a persistent filling defect due to oedema from that caused by a pathological lead point or an incompletely reduced intussusception[166,167], and problems in the identification of free air reflux in the presence of gaseous small bowel dilatation[62]. In isolation, free reflux of barium or gas into the distal ileum does not completely exclude the possibility of a residual ileocolic intussusception[166,168] or an ileoileal component[138,142], so observation over the ensuing 24 h is mandatory. Persistence of clinical signs or a residual filling defect on postevacuation radiography is an indication for laparotomy, albeit through a Lanz gridiron incision.

In the stable patient, some authors have recommended a second attempt at radiological reduction[16,67]. This appears to be safe and justifiable in the stable, resuscitated infant during a period of up to 2 h after the first attempt[16,67], particularly when the intussusception has been reduced to the caecum. We are against later attempts at non-operative reduction[149] because of the rapidity of clinical deterioration in some infants, and recommend early laparotomy.

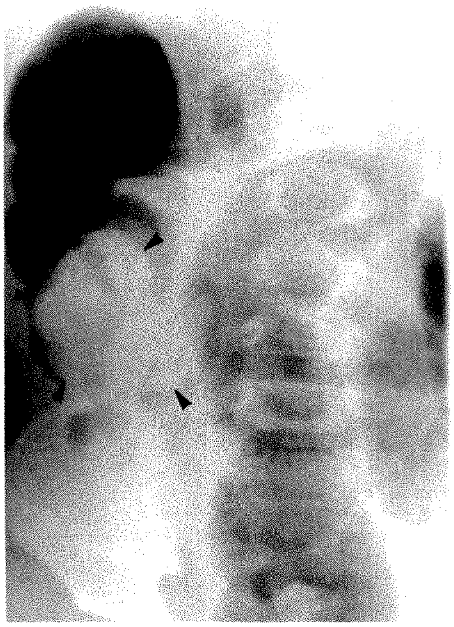

**Figure 4** *Radiograph following an air contrast enema, outlining an ileocolic intussusception during reduction. The intussusceptum (arrowed) has been reduced to the caecum*

There have been some recent reports of successful ultrasonographic monitoring of hydrostatic[162,169] or pneumatic[145] reduction procedures in an effort to eliminate exposure to ionizing radiation. Successful reduction in 95 per cent of 377 patients, with no deaths and with only one colonic perforation, was reported in one series[162].

### *Operative reduction*

Operative reduction is necessary for those in whom radiological techniques are contraindicated or have failed, when a pathological lead point is suspected, or in the case of multiple recurrences.

Various incisions have been employed but a right transverse muscle cutting incision, either just above or below the umbilicus, is associated with fewer complications than a vertical incision[170]. The intussusception is gently 'milked' back by compression of its apex. Sustained pressure to reduce the oedema of the intussusceptum may help and packs should be carefully placed to minimize peritoneal contamination from toxic fluid escaping from within the invagination. The reduced bowel should be allowed time to recover perfusion. Both the intussusceptum and the intussuscipiens must be carefully inspected for areas of doubtful viability. Seromuscular tears of the intussuscipiens with viable margins may be oversewn. Irreducible intussusceptions or those complicated by infarction or a pathological lead point require resection and primary end-to-end anastomosis[171]. Resection rates vary widely (*Table 6*) and partly reflect the experience of the surgeon and delay in presentation[17,112]. With modern antibiotics there are few indications for stoma formation.

If the caecum appears healthy, many surgeons perform an appendicectomy (either by excision or inversion), purportedly to encourage fixation of the caecum[124,172], to avoid future confusion as to whether or not appendicectomy was performed[170] and to prevent appendicitis. With increasing use of the appendix as a conduit in reconstructive surgery and the declining mortality rate from appendicitis, this procedure has to be questioned[173]. The recurrence rate after simple operative reduction is very low (*Table 6*) and most surgeons do not make any attempt to fix the caecum or terminal ileum, there being scant evidence to support such procedures. In the presence of associated intestinal malrotation, Ladd's procedure, which achieves a more stable mid-gut mesentery, should be considered[60]. In some cases a reperfusion injury[174] appears to complicate the operative treatment of ischaemic intussusception, and the protective role of free radical scavengers, such as mannitol, deserves investigation.

**Table 6** *Recent results of operative treatment of intussusception*

| Reference | Year | Place | No. of patients undergoing laparotomy | Resection rate* (%) | Postoperative recurrence rate (%) | Perioperative mortality rate (%) |
|---|---|---|---|---|---|---|
| Hutchison *et al.*[42] | 1980 | Glasgow | 163 | 17 | — | 1·8 |
| Pollet[104] | 1980 | Aberdeen | 70 | 6·5 | 2·9 | 0 |
| Man *et al.*[113] | 1983 | South-east England | 69 | 9 | 2·9 | 0 |
| Sparnon *et al.*[23] | 1984 | Australia | 84 | 9 | 2·4 | 1·6 |
| Liu *et al.*[67] | 1986 | Dublin | 25 | 4·5 | 4·0 | 0 |
| Mackay *et al.*[24] | 1987 | Australia | 21 | 3·3 | 0 | 0 |
| Winstanley *et al.*[114] | 1987 | Manchester | 51 | 14 | 2 | 2 |
| Zamir *et al.*[138] | 1987 | Israel | 32 | 11·5 | 0 | 0 |
| Wilson-Storey *et al.*[61] | 1988 | Edinburgh | 94 | 8 | 1·1 | 0 |
| Skipper *et al.*[141] | 1990 | USA | 64 | 19 | 3·1 | 1·6 |

*Resection rate expressed as a percentage of patients presenting with intussusception

Even though intussusception following operation may affect multiple sites, surgical reduction is curative and pathological lead points and recurrences very rare[79]

## Mortality, morbidity and recurrence

In the 19th century intussusception was usually fatal, but after the popularization of radiologically controlled contrast enema reduction the mortality rate declined to under 10 per cent and is now less than 1 per cent overall[20]. Avoidable factors still occur in 60 per cent of deaths[20]. Morbidity and mortality rates are higher when there is delay in presentation or treatment[42,175], typically in older children and in small bowel intussusceptions[2,20,76,176].

Adhesive intestinal obstruction features as a late complication in 3–6 per cent of patients undergoing operative reduction[17,61,67,104,113,120] but has not been reported after hydrostatic reduction.

Recurrent intussusception occurs in about 4 per cent of patients[22,32,177]. After radiological or operative reduction, the respective recurrence rates are about 10 per cent and 1–4 per cent[22,23,32,67,89,113,172]. Recurrence may be detected within days of hydrostatic reduction[32] but rarely so soon after operative reduction. Most recurrences develop within 1–36 months after reduction, with a peak incidence[32,177] during the eighth month. With all recurrent intussusceptions an underlying abnormality must be considered, but most first recurrences are not due to a pathological lead point and can be successfully managed by hydrostatic reduction[32,172].

In patients with multiple recurrences, structural anomalies in the ileocaecal region are common. Focal lymphoid hyperplasia of the ileum may be present[32,87,178] and, very frequently, an excessively mobile caecum attached to the posterior abdominal wall by a mesentery. Second recurrences should be managed by operative reduction but further invaginations are best treated by limited ileocaecal resection with end-to-end anastomosis[172]. Attempts have been made to stabilize the ileocaecal region by various plication procedures, such as suturing the terminal ileum to the ascending colon or using the base of the caecum as a temporary caecostomy[32,178–180], but the limited experience of the authors accords with that of Kyle *et al.*[177] who found that in some patients these procedures may even be harmful.

Improvements in the management of childhood intussusception are likely to be gained from wider awareness of its varied presentations, attention to detail in resuscitation, and prompt referral of the patient to a centre with combined paediatric radiological, anaesthetic, surgical and nursing expertise.

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# Perforated duodenal diverticulum

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*Duodenal diverticula are present in up to 20 per cent of the population but few patients require surgery for acute complications. Perforation is the rarest of these complications; only 101 affected patients have been reported in the world literature. These reports of perforated duodenal diverticulum are reviewed and strategies for the diagnosis and management of this unusual condition are discussed.*

Since the incidence of duodenal diverticulum is second only to that of diverticulum of the colon, it is surprising that this lesion does not become symptomatic more often. The clinical presentation is non-specific and the diagnosis one of exclusion. Spontaneous perforation of a duodenal diverticulum is extremely rare: just over 100 cases have been reported in the world literature. Of these, only 13 were proven before operation by radiographic studies. Almost all of the reported cases required surgical treatment.

## History and pathophysiology

The first description of a duodenal diverticulum found at autopsy was made by Chomel in 1710[1,2]. More than 200 years later, in 1916, Case demonstrated the condition on a radiograph[3]. In 1915, Forsell and Key diagnosed a diverticulum on an upper gastrointestinal radiograph using contrast agent and performed the first successful duodenal diverticulectomy[1]. As these radiographic studies became more frequently used, the reported incidence of duodenal diverticulum increased: it has varied from 1 to 5 per cent in upper gastrointestinal radiographic studies[4–6] and post-mortem analyses have shown incidences of up to 22 per cent[6–8].

The aetiology of the duodenal diverticulum remains unknown. The most widely accepted theory, however, implicates a weakness of the intestinal wall[1,4,8]. Diverticula are usually classified into three types. A true congenital diverticulum includes all the layers of the intestinal wall. This is the rarest type and is thought to result from an abortive attempt to form a supernumerary pancreas[8]. Only two perforations of a true congenital diverticulum have been reported[9]. Primary acquired pulsion diverticulum, or pseudo-diverticulum, is the commonest type Possibly, these diverticula protrude through the weak areas of intestinal wall where blood vessels penetrate and contain only mucosal and serosal layers[1,4,7]. An alternative theory is that increased intraluminal duodenal pressure occurs secondary to a chronic duodenal obstruction caused by the superior mesenteric vessels crossing over the bowel[10]. Secondary acquired diverticulum is the second commonest type and is believed to be caused by traction on a particular area of the duodenum by scarring or adhesions from a previous local inflammatory reaction (cholecystitis, lymphadenitis or duodenal ulcer). This type contains all the layers of the intestinal wall and is not a true diverticulum, simply an outpouching of the intestinal lumen. Secondary diverticula are found most frequently in the first part of the duodenum[1,2,11].

Most duodenal diverticula (88 per cent) are located along the pancreatic or mesenteric border, supporting the theory that they are caused by a weakness in the intestinal wall[2]. Approximately two-thirds are located in the second part of the duodenum and many are imbedded in the pancreas[2,4]. Most are within 2·5 cm of the ampulla of Vater and are therefore known as perivaterian; 16 per cent are multiple[4].

## Clinical presentation

The clinical diagnosis of diverticulum of the duodenum is difficult because there is no characteristic presentation. Symptoms are vague and non-specific, and lead the surgeon to consider other more common diseases such as cholecystitis, cholelithiasis, duodenal ulcer, gastritis and pancreatitis. The diagnosis is thus one of exclusion.

Duodenal diverticula are commonly associated with other lesions of the gastrointestinal tract, such as diverticula elsewhere in the bowel, biliary tract disease, peptic ulcer and hiatus hernia[2]. The high incidence of other gastrointestinal diseases is probably related to the age of affected patients. Most are at least 50 years old, although perforation has been reported in a child and in a teenager[12,13]. Not all diverticula are symptomatic, indeed most run a benign course, only 10 per cent having clinical relevance[4]. One isolated study has reported that 74 per cent of duodenal diverticula cause serious symptoms[14]

The possible complications of duodenal diverticula are· common bile duct obstruction with cholangitis or jaundice, acute and chronic recurrent pancreatitis; partial duodenal obstruction; diverticulitis or peridiverticulitis; ulceration with or without haemorrhage; fistula to adjacent organs including the gallbladder, common bile duct, colon and aorta; enterolith formation with distal small intestinal obstruction or penetration into adjacent organs; malignant degeneration; torsion of the diverticulum; diarrhoea secondary to a blind loop syndrome, and perforation[10,11,15–17]

## Perforation

Perforation is considered to be the most serious complication but fortunately it is also the rarest; only 101 patients so affected have been reported in the world literature. Juler *et al.*[11] in 1969 published a collection of 56 cases and an additional 45 from the world literature are reported here (*Table 1*). All of the following data are from the total of 101 patients, except where otherwise stated.

In most patients (57 per cent) diverticulitis precedes and causes the perforation. This diverticulitis follows stasis and peptic digestion[11]. The smaller the stoma into the diverticulum, the more likely it is that stasis will occur[49]. Other causes of perforation (*Table 2*) include enterolithiasis, ulceration, increased intraluminal pressure, presence of a foreign body, blunt abdominal trauma and the presence of a gallstone

Perforation of a duodenal diverticulum has no pathognomonic signs or symptoms. In most patients (78 per cent) the onset is acute with pain localized to the right upper abdomen or epigastrium, and associated nausea and vomiting. Some patients present with chronic abdominal pain, anorexia and malaise, which may have lasted as long as 1 month Three patients in the literature reports presented with a history of months of steatorrhoea secondary to duodenocolic fistulae[19,29,34].

The sequelae of perforation include retroperitoneal abscess,

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**Table 1** *Reported cases of perforated duodenal diverticulum, 1969–1990*

| Reference | Year | Age (years) | Sex | Symptom onset | Preoperative diagnosis | Part of duodenum | Area of perforation | Cause of perforation | Treatment | Complications | Result | Radiographic findings* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Turner[18] | 1969 | 27 | F | Acute | Acute cholecystitis | 2nd | Retroperitoneum | Enterolith | Diverticulectomy | Intra-abdominal abscess | Survival | Enterolith (retrospective) |
| Dey and Latchmore[19] | 1970 | 55 | M | Chronic | Duodenocolic fistula | 3rd | Ascending colon | Ectopic gastric mucosa | Diverticulectomy | None | Survival | UGI/LGI fistula |
| Graudins[20] | 1970 | 70 | F | Acute | Perforated viscus | 2nd | Retroperitoneum | Trauma (enterolith) | Diverticulectomy | Shock | Death | n a |
| Reilly and Kune[21] | 1970 | 59 | F | Acute | n a | 2nd | Retroperitoneum | Increased intraluminal pressure | Diverticulectomy | None | Survival | n a |
| Reilly and Kune[21] | 1970 | 44 | M | Acute | n a | 2nd | Retroperitoneum | Increased intraluminal pressure | Diverticulectomy | None | Survival | Normal |
| Cavanagh[22] | 1970 | 51 | F | Acute | Perforated viscus | 2nd | Retroperitoneum | Enterolith | Tube duodenostomy/ drainage | None | Survival | Normal |
| Miller *et al.*[23] | 1970 | 78 | F | Acute | Acute cholecystitis | n.a | Pancreas | n a. | No surgery | Sepsis | Death | Ileus, RUQ calcification |
| Wolfe and Pearl[24] | 1972 | 69 | F | Acute | Perforated viscus | 2nd | Retroperitoneum | Diverticulitis/gangrene | Diverticulectomy/ drainage/BII | n a | n a | Air in paraduodenal area |
| Blomstedt and Holm[25] | 1972 | 61 | F | Acute | n a | 2nd | Retroperitoneum | Diverticulitis/foreign body | Diverticulectomy/ drainage | Retroperitoneal fistula | Survival | Retroperitoneal air<br>UGI normal |
| Peutz *et al*[12] | 1973 | 77 | M | Acute | Perforated ulcer | n a | Retroperitoneum | Diverticulitis | Diverticulectomy/ drainage | None | Survival | Normal |
| Peutz *et al*[12] | 1973 | 33 | F | Acute | Acute cholecystitis | 2nd | Retroperitoneum | Enteroliths | Diverticulectomy/ drainage | None | Survival | Chest radiograph normal |
| Peutz *et al*[12] | 1973 | 5 | M | Chronic | Tumour | 2nd | Pancreas | Diverticulitis | Diverticulectomy/ drainage | None | Survival | n.a |
| Scarpa *et al*[26] | 1974 | 73 | F | Acute | Perforated viscus | 2nd | Retroperitoneum | Diverticulitis | Diverticulectomy/ omental patch/ drainage | None | Survival | RUQ calcification |
| Dippon[27] | 1974 | 79 | F | Acute | Mesenteric ischaemia | 2nd | Retroperitoneum | n.a | Diverticulectomy | None | Survival | Retroperitoneal air (retrospective) |
| Sicard *et al*[28] | 1974 | 86 | F | Acute | Colonic cancer, cholecystitis, appendicitis | 2nd | Retroperitoneum | Diverticulitis | Diverticulectomy | Enterocutaneous fistula | Death | Normal |
| Sicard *et al*[28] | 1974 | 80 | F | Acute | Appendicitis, cholecystitis | 2nd | Anterior | n.a | Diverticulorrhaphy/ drainage | None | Survival | n a |
| de Medeiros *et al*[9] | 1975 | 57 | M | Acute | n a. | 2nd | Anterior | n a | Diverticulectomy/ drainage | Respiratory failure | Death | Normal |
| de Medeiros *et al.*[9] | 1975 | 70 | F | Chronic | Perforated viscus | 2nd | Retroperitoneum | n a | Diverticulectomy/ drainage/BII | Pneumonia, duodenal fistula | Survival | Free air<br>UGI. diverticulum |
| Kellum *et al*[29] | 1976 | 37 | M | Chronic | Duodenocolic fistula | 3rd | Transverse colon | Diverticulitis | Diverticulectomy/ serosal patch | None | Survival | UGI/LGI fistula, diverticulum |
| Ettman and Kongtawng[30] | 1977 | 54 | M | Acute | Upper gastrointestinal bleeding/pancreatitis | 2nd | Pancreas | Diverticulitis | Whipple procedure | Pancreatic and small bowel fistulae | Death | UGI fistula, free air, diverticulum |
| Widdershoven[31] | 1977 | 38 | F | Acute | n a | 2nd | Retroperitoneum | Diverticulitis/enterolith | Diverticulectomy | None | Survival | n a |
| Hansen and Taudorf[15] | 1977 | 75 | F | Acute | Acute cholecystitis | 3rd | Retroperitoneum | Diverticulitis | n a. | n a | n a | Retroperitoneal air |
| Glasser *et al*[32] | 1978 | 49 | F | Chronic | Perforated duodenal diverticulum | 2nd | Anterior | Diverticulitis | Diverticulectomy | None | Survival | Paraduodenal air<br>UGI· diverticulum |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Donald[33] | 1979 | 56 | M | Acute | Perforated ulcer | 2nd | Retroperitoneum | n a. | Diverticulectomy/ drainage | Duodenal fistula | Survival | Normal |
| Donald[33] | 1979 | 70 | F | Acute | n a | 2nd | Retroperitoneum | n.a | Diverticulectomy/ vagotomy/BII | None | Survival | UGI diverticula |
| Yasui *et al.*[34] | 1979 | 50 | F | Chronic | Duodenocolic fistula | 2nd | Ascending colon | n a. | n.a. | None | Survival | UGI. fistula, diverticulum |
| Yasui *et al.*[34] | 1979 | 73 | M | Chronic | Duodenocolic fistula | 2nd | Hepatic flexure | n a. | n.a. | None | Survival | UGI/LGI fistula, diverticulum |
| Vorster and Tataru[35] | 1980 | 68 | F | Acute | n a. | 2nd | Retroperitoneum | Diverticulitis | Diverticulectomy | None | Survival | n a. |
| Cox[36] | 1980 | 32 | F | Acute | Acute cholecystitis | 2nd | Retroperitoneum/ pancreas | Diverticulitis | Diverticulectomy | Duodenal fistula | Survival | Normal<br>UGI: normal |
| Manny *et al*[14] | 1981 | n a. | n a. | n.a. | n a. | n a. | n a | Diverticulitis | Diverticulectomy | Duodenal fistula | Survival | n a. |
| Manny *et al.*[14] | 1981 | n a | n a. | n a | n.a. | n a. | n.a. | Diverticulitis | Diverticulectomy | Duodenal fistula | Survival | n a. |
| Scudamore *et al.*[37] | 1982 | 85 | M | Acute | Perforated viscus | n a | n.a. | Gallstones | Diverticulectomy | Pancreatitis | Survival | Paraduodenal air |
| Scudamore *et al.*[37] | 1982 | 87 | F | Acute | Perforated viscus | 2nd | n a | n.a | Tube duodenostomy/ omental patch/ drainage | Duodenal fistula | Survival | Normal |
| Wells[38] | 1983 | 55 | M | Chronic | n a | 2nd | Anterior | Increased intraluminal pressure | Drainage | None | Survival | UGI diverticula<br>US pancreatic mass |
| Zamir *et al*[39] | 1984 | 72 | F | Acute | Acute cholecystitis | 2nd | Retroperitoneum | Diverticulitis | Diverticulectomy/tube duodenostomy/ drainage | None | Survival | n a. |
| Haugh and McBee[40] | 1984 | 61 | M | Acute | Acute cholecystitis | 2nd | Retroperitoneum | n a. | Diverticulectomy/ drainage | Intra-abdominal abscess | Survival | Normal |
| Stebbings and Thomson[41] | 1985 | 67 | M | Acute | Small bowel obstruction | n a. | Retroperitoneum | n.a. | Diverticulectomy/ drainage | Duodenal fistula | Survival | Ileus |
| Stebbings and Thomson[41] | 1985 | 89 | F | Acute | Unknown | n.a | Retroperitoneum | n.a | Diverticulectomy/ drainage | None | Survival | Normal |
| Beech *et al*[42] | 1985 | 64 | F | Acute | Perforated duodenal diverticulum | 2nd | Retroperitoneum | Diverticulitis | Tube duodenostomy/ drainage, 6 weeks later, diverticulectomy | Metabolic alkalosis | Survival | Retroperitoneal air<br>UGI. diverticulum with extravasation and paraduodenal mass |
| Tissot *et al.*[43] | 1988 | 71 | M | Acute | Perforated duodenal diverticulum | 2nd | Lesser sac | n a. | Diverticulectomy/ drainage | None | Survival | UGI: diverticulum with extravasation<br>CT. abscess |
| El Khatib[44] | 1988 | 70 | M | Acute | Perforated ulcer | 2nd | Retroperitoneum | Diverticulitis | Diverticulectomy/ drainage | None | Survival | Normal |
| Vanek *et al*[45] | 1989 | 70 | F | Acute | Perforated ulcer | 2nd | Retroperitoneum | Enterolith | Diverticulectomy | Wound infection | Survival | Normal |
| Perrott[46] | 1989 | 69 | F | Acute | Acute cholecystitis | 2nd | Retroperitoneum | n.a | Drainage | Sepsis | Death. | UGI: diverticulum |
| Van Beers *et al*[47] | 1989 | 77 | M | Acute | Perforated duodenal diverticulum | 4th | Retroperitoneum | n a. | No surgery | None | Survival | UGI/CT perforated diverticulum |
| Goodman *et al*[48] | 1989 | 52 | F | Acute | Perforated duodenal diverticulum | 4th | Retroperitoneum | Diverticulitis | Diverticulectomy | None | Survival | CT: perforated diverticulum |

*Radiography was plain abdominal unless specified n a , Not addressed in reference paper BII, Billroth II gastrojejunostomy; UGI, upper gastrointestinal contrast radiography; LGI, lower gastrointestinal contrast radiography, RUQ, right upper quadrant of abdomen; US, ultrasonography of abdomen; CT, computed tomography

**Table 2** *Causes of duodenal diverticular perforation in 101 patients*

| Cause of perforation | No. in series of Juler *et al.*[11] | No. in present series | Total* |
|---|---|---|---|
| Diverticulitis | 40 | 19 | 59 (57) |
| Enterolithiasis | 6 | 6 | 12 (12) |
| Ulceration | 9 | 0 | 9 (9) |
| Increased intraluminal pressure | 0 | 3 | 3 (3) |
| Foreign body | 1 | 1 | 2 (2) |
| Trauma | 0 | 1 | 1 (1) |
| Gallstone | 0 | 1 | 1 (1) |
| Unknown/not specified | 0 | 16 | 16 (16) |

Values in parentheses are percentages. *Two patients had more than one cause specified, giving a total of 103

**Table 3** *Preoperative diagnoses considered in patients with perforated duodenal diverticula*

| Preoperative diagnosis | No. in series of Juler *et al.*[11] | No. in present series | Total |
|---|---|---|---|
| Cholecystitis | 15 | 10 | 25 (26) |
| Perforated ulcer | 12 | 4 | 16 (17) |
| Perforated duodenal diverticulum | 3 | 5 | 8 (8) |
| Appendicitis | 7 | 2 | 9 (9) |
| Perforated viscus | 0 | 7 | 7 (7) |
| Duodenocolic fistula | 0 | 4 | 4 (4) |
| Bowel obstruction | 2 | 1 | 3 (3) |
| Upper gastrointestinal bleed | 2 | 1 | 3 (3) |
| Colonic cancer/tumour | 0 | 2 | 2 (2) |
| Mesenteric ischaemia | 0 | 1 | 1 (1) |
| Pancreatitis | 0 | 1 | 1 (1) |
| Unknown/not specified | 5 | 11 | 16 (17) |

Values in parentheses are percentages

**Table 4** *Area of perforation of duodenal diverticula*

| Location of perforation | No. in series of Juler *et al*[11] | No. in present series | Total* |
|---|---|---|---|
| Retroperitoneum | 43 | 29 | 72 (70) |
| Pancreas | 4 | 4 | 8 (8) |
| Colon | 3 | 4 | 7 (7) |
| Anterior | 2 | 4 | 6 (6) |
| Gallbladder | 3 | 0 | 3 (3) |
| Aorta | 2 | 0 | 2 (2) |
| Lesser sac | 0 | 1 | 1 (1) |
| Unknown/not specified | 0 | 4 | 4 (4) |

Values in parentheses are percentages. *Two patients had more than one location specified, giving a total of 103

sepsis, mediastinitis[27], duodenocolic fistula with steatorrhoea[19,29,34], and gastrointestinal tract bleeding secondary to perforation into the aorta[11].

In most instances the preoperative diagnosis is incorrect. The most common erroneous diagnoses considered are cholecystitis, perforated viscus and appendicitis (*Table 3*). A correct preoperative radiographic diagnosis was made in 13 of the 101 patients. Plain abdominal radiographs may show periduodenal or retroperitoneal air, or they may be entirely normal. If the diverticulum perforates anteriorly, the radiograph may demonstrate a pneumoperitoneum. Fifty per cent of the plain radiographs obtained in this series were normal; only 27 per cent demonstrated retroperitoneal or paraduodenal air. Upper gastrointestinal radiographic studies may show a diverticulum with extravasation of contrast medium Eighty per cent of such studies obtained in this series showed a diverticulum, but only seven of these demonstrated a fistula or extravasation of contrast medium. In three cases the diagnosis was confirmed by the use of abdominal computed tomography[43,47,48], and endoscopic retrograde cholangiopancreatography confirmed the diagnosis in one[43]. The duodenocolic fistulae were demonstrated by upper and lower gastrointestinal radiographic contrast studies.

Juler *et al.*[11] found that eight of 56 perforated duodenal diverticula were missed during operation up to 1969. The present series of 45 patients included only a single missed perforation, perhaps because surgeons today are more aware of perforated duodenal diverticulum as a pathological entity Juler *et al.* also reported an additional eight perforated diverticula diagnosed at autopsy without previous surgical intervention Two cases of perforation diagnosed only at autopsy[23,46] are reported here.

According to Juler *et al.* the mortality rate associated with perforated duodenal diverticulum from 1907 to 1969 was 34 per cent. Even in recent times, with increased awareness and improved preoperative and intraoperative diagnosis of this condition, there is still a mortality rate of 13 per cent in the series from 1969 to the present. This high rate may be caused in part by the advanced age of the patients and associated underlying diseases. Most perforations occur retroperitoneally, but the diverticulum may also perforate anteriorly, or into the pancreas, colon, gallbladder or aorta (*Table 4*).

## Management

Surgical treatment is required for only 1–2 per cent of duodenal diverticula[2,4,5,49]; diverticulectomy with two-layer closure of the duodenum is the treatment of choice[4]. Special care should be taken to avoid injury to the distal common bile duct and ampulla of Vater because most diverticula arise in this area. If perforation has occurred, the retroperitoneum should be drained

Complications of operations to repair the 46 perforated duodenal diverticula occurred in 41 per cent of the 45 patients in the present series. The most common complication was duodenal fistula (20 per cent) Two patients (4 per cent) had an intra-abdominal abscess, and five (11 per cent) had continued sepsis or sepsis-related complications. Pancreatitis developed after operation in one patient (2 per cent), and one sustained a wound infection.

Reports have been made on two patients who were successfully treated with conservative therapy alone[47,50] Juler *et al*[11] previously described two cases managed non-operatively[50,51]; however, after reviewing the original reports it is clear that the patient described by Fischer[51] in 1958 actually had a cholecystoduodenal fistula that initially mimicked a perforated duodenal diverticulum on radiography. The patient reported by Shackleton[50] in 1963 had a perforated duodenal diverticulum demonstrated by upper gastrointestinal radiography. The perforated duodenal diverticulum reported by Van Beers *et al.* in 1989 was documented by computed tomography[47]. Both patients improved initially with intravenous fluids and parenteral antibiotics. Because of their improvement with conservative therapy, their advanced ages and underlying medical problems, non-operative therapy was continued. Both patients recovered.

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# Anatomy and function of the anal longitudinal muscle

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*The longitudinal muscle in the intersphincteric space has received little attention despite an explosion of interest in anorectal physiology in the past decade. Its anatomy is contested and its function unknown. Speculation, however, gives it a role as a skeleton supporting and binding the rest of the internal and external sphincter complex together, as an aid during defaecation by everting the anus, as a support to the haemorrhoidal cushions, and as a determining factor in the ramification of sepsis.*

The longitudinal muscle of the anal canal has been neglected by most surgeons, but in an age of rapidly advancing laboratory and clinical investigative techniques more attention should be afforded to this ill-understood structure. It can be seen during intersphincteric approaches to the anorectum, imaged by endoanal ultrasonography and magnetic resonance techniques, and some aspects of its pharmacological behaviour have recently been investigated[1]. We cannot hope fully to understand any possible functions of the muscle, however, without a fundamental knowledge of its anatomy, and it is in this respect that agreement is lacking. Although the adjacent muscle bulks of the internal and external anal sphincters have the predominant roles, the integrated function of the whole sphincter complex may be appreciated only by a greater understanding of the muscle that binds and braces the components of the anal canal together.

Confusion and seemingly irreconcilable differences in descriptions of the same structure stem from various sources. First, there is a great problem with nomenclature and an overabundance of eponyms. Up to three names may be ascribed to the same structure and names applied to one structure are used in the description of others. Second, descriptions in one plane cannot explain the anatomy of a complex three-dimensional organ. Studies of cadaveric specimens and those retrieved at operation do not necessarily reflect the relations that exist in the living subject. Finally, differences due to age, sex, and individual variation are often not taken into account.

## Origin and intersphincteric course

The longitudinal muscle of the anal canal is a direct continuation of the outer muscle coat of the rectum, augmented by striated muscle fibres that have been described as originating from a variety of sources (*Table 1*). More muscle bundles are seen histologically in the fetal anal canal, with a gradual replacement of muscle by fibrous and elastic connective tissue with age, but it remains unclear to what level striated muscle derived from the pelvic floor muscles descends in the intersphincteric space. Kerremans[8] is alone in describing ascending as well as descending muscle fibres in the intersphincteric space, these fibres, in his opinion, crossing the whole striated circumanal musculature. Shafik[6] considers the conjoined muscle to pass down in three layers, each from a separate origin and separated from each other by fascial septa (*Figure 1*).

## Medial extensions

Both Rudinger[9] in 1878 and Roux[10] 3 years later described fibres crossing the internal sphincter and forming a connection between the submucosal and intersphincteric layers. Rudinger suggested that it was the fibres originating in the submucosal muscle layer that traversed the sphincter and Roux that these fibres were derived from the longitudinal muscle layer. More recently, Kerremans[8] and Lawson[11] attributed their origin to the internal sphincter itself. Rudinger and Roux also described arches of longitudinal muscle fibres running to join the submucosal muscle fibres around the distal border of the internal sphincter (*Figure 2*). Milligan and Morgan[3] named the medial extension which passed between the internal and subcutaneous external sphincters to insert into the anal skin at the mucocutaneous junction the 'anal intermuscular septum'. Its position marked the upper border of the subcutaneous

**Table 1** *Descriptions of the derivation of fibres augmenting the outer muscle coat to form the conjoined longitudinal muscle of the anal canal*

| Reference | Description |
|---|---|
| Cruveilhier[2] | Levator ani |
| Milligan and Morgan[3] | Puborectalis posteriorly, deep external anal sphincter anteriorly |
| Courtney[4] | Levator fascia; muscle fibres from the inferior and superior surfaces of puborectalis, pubococcygeus, iliococcygeus |
| Lawson[5] | Lower fibres of puboanalis |
| Shafik[6] | Pubococcygeus; top loop of the external anal sphincter |
| Ayoub[7] | Pelvic layer of the anterior fibres of levator ani |

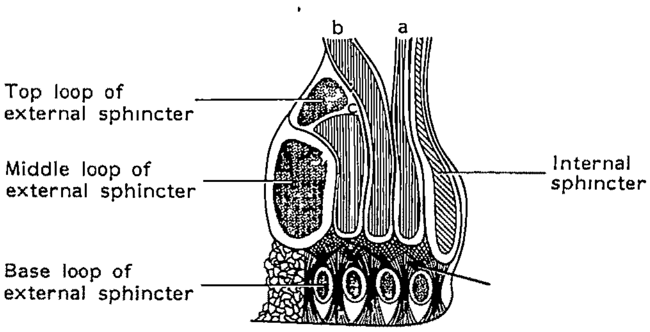
b
a
Top loop of external sphincter
Middle loop of external sphincter
Base loop of external sphincter
Internal sphincter

**Figure 1** *Structure of the longitudinal muscle and the related fascial septa (according to Shafik[6]) The medial longitudinal muscle (a) is a direct continuation of the outer muscle coat of the rectum, the intermediate layer (b) is a direct prolongation of the pubococcygeus (and therefore does not exist anteriorly) and the lateral longitudinal muscle (c) is an extension of the top loop of the external sphincter, again deficient anteriorly Shafik describes six fascial septa in relation to the muscles of the anal canal which converge at the central tendon (arrowed), from which septa arise which fan out between the bundles of the base loop inferiorly, and which form a loose collagen network in the fat of the lower ischiorectal fossa laterally*

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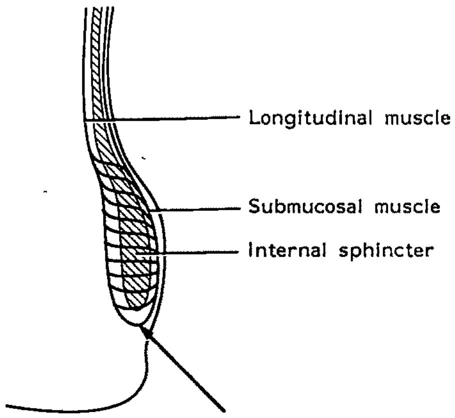

**Figure 2** *Crossing of the internal sphincter by fibres derived from the longitudinal muscle layer which contribute to the smooth muscle of the submucosa (as described by Roux*[10]*) The arch of longitudinal muscle fibres which passes around the distal border of the internal sphincter (arrowed) was later named the anal suspensory ligament*[3]

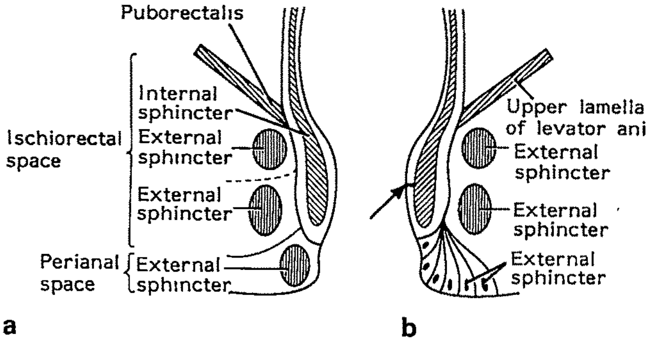

**Figure 3** *Differences between concepts of* **a** *Milligan and Morgan and* **b** *Parks of the longitudinal muscle of the anal canal and the spaces created by its extensions The mucosal suspensory ligament of Parks (arrowed) creates an extra space (the marginal space) separating the submucous and perianal spaces In* **a**, *the perianal space is continuous with the ischiorectal fossa; in* **b**, *it is contained within the inferior extensions of the longitudinal muscle. Note also in* **a** *the upper (inconstant) and the lower (constant) outward extensions of the longitudinal muscle dividing the external sphincter into its component parts*

external sphincter, the muscle thought to be divided for treatment of recurrent fissure *in ano*. It also divided the space between epithelium and muscle into an upper submucous and a lower perianal space, the latter continuous laterally with the ischiorectal fossa (*Figure 3*). By contrast, Parks[12] believed the groove between the superior and inferior haemorrhoidal plexuses to be caused by fibrous tissue derived from the sheath surrounding the internal anal sphincter. This sheath passed medially to be inserted into the mucosa of the anal crypts as a band, named by him the 'mucosal suspensory ligament'. This marked the upper limit of a 'marginal' space, itself confined laterally by the inferior extensions of the longitudinal muscle layer inserting into the perianal skin and separating the perianal space from the ischiorectal fossa.

Some have found no specific circumferential attachment of longitudinal muscle fibres at the intersphincteric groove[13,14]; others have agreed with Milligan and Morgan in their descriptions of a thickened band of fibres passing between the internal and subcutaneous external sphincters to attach to the anal canal in the region of the pecten[4]. Furthermore, extensions from this band have been noted to pass upwards in the submucosa to contribute to the submucosal muscle layer, supplementing those derived from the same longitudinal muscle origin which entered the submucosal space at a higher level. The submucosal muscle, variously named the 'musculus canalis ani'[15], 'sustentator tunicae mucosae'[16], 'Treitz's muscle'[17] and 'musculus submucosae ani'[18], appears to give support to the anal mucosa through its connections with the deeper layers of the sphincter complex[19].

## Outward extensions

There is debate not only about the longitudinal muscle but also about the arrangement of the external sphincter complex. Some of this debate is semantic, but much is caused by different descriptions of the outward extensions from the intersphincteric longitudinal muscle layer which divide the external sphincter into its various subdivisions. Abel[20] illustrated the relations of the anal canal from sections lent by Cuthbert Dukes and showed the longitudinal muscle passing in two layers, one through the external sphincter, dividing it into superficial and deep parts, and the second around the sphincter, forming a capsule for it (*Figure 4*). In accordance with Santorini's division of the external sphincter into three parts over 150 years earlier[14], Milligan and Morgan described two septa. One is constant, passing between the superficial and subcutaneous components, and the other inconstant, passing between the superficial and deep components. Each becomes lost in the ischiorectal fat (*Figure 3*). The constant lower septum divides the ischiorectal fossa into a superficial perianal space and a deeper ischiorectal space[21].

Courtney[4] described longitudinal muscle fibres that separate the bundles of the external sphincter throughout its length, filamentous as they traverse the deeper aspects of the sphincter and fat of the ischiorectal fossa, but much thicker in the more superficial parts (*Figure 4*). Kerremans[8] also noted fibres passing out from the intersphincteric layer to divide puborectalis and the deeper parts of the external sphincter into several components. However, others have found no evidence of any division of these areas by extensions derived from the longitudinal muscle[11,22]. Nevertheless, there is general agreement that the subcutaneous portion of the sphincter is anatomically separate from the rest, by virtue of the longitudinal muscle extensions that pass around and through it to insert into the anal and perianal skin.

Oh and Kark[23] noted differences in the arrangement of the external sphincter according to sex and site around the circumference of the anal canal. In the male, the upper half of the external sphincter is enveloped anteriorly by the conjoined longitudinal muscle, while the lower half is crossed by it. In the female, the whole of the external sphincter is encapsulated anteriorly by a mixture of longitudinal muscle fibres and anteriorly projecting fibres derived from the internal anal sphincter. Outside the external sphincter, Courtney[4] described extensions of the longitudinal muscle encircling the urethra as the sphincter urethrae, contributing laterally to the puboprostatic ligament and helping posteriorly to form the ileorectococcygeus muscle. He deduced from this arrangement that at one time fibres from the longitudinal muscle layer must have extended to the bony pelvis around its entire

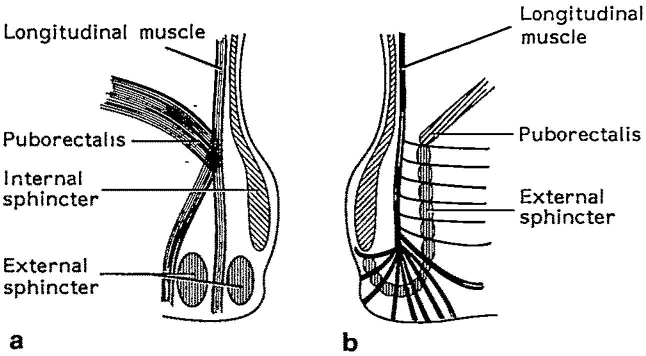

**Figure 4** *Differences in relations of the longitudinal muscle and the external sphincter as described by* **a** *Abel*[20] *and* **b** *Courtney*[4]. *In* **a** *the external sphincter is encapsulated by longitudinal muscle fibres, whereas in* **b** *the whole length of the sphincter is split by longitudinal muscle fibres passing out into the ischiorectal fossa*

**Table 2** *Differences in descriptions of corrugator cutis ani muscle, demonstrating the variation in understanding of its nature*

| Reference | Description |
|---|---|
| Last[26] | Remnant of the panniculus carnosus |
| Milligan and Morgan[3] | Downward fascial extension of the anal intermuscular septum |
| Wilde[14] | Fibroelastic ramifications of the conjoined longitudinal muscle coat |
| Goligher *et al* [13] | Extension of the musculus submucosae ani |
| Buchanan[27] | Synonymous with the subcutaneous external anal sphincter |
| Fowler[22] | Structure does not exist |
| Shafik[6] | Terminations of the intermediate septa derived from the central tendon |

circumference Several authors describe anterior extensions contributing to the rectourethralis muscle[11,24,25].

## Inferior extensions

Most authorities accept that the main bulk of the conjoined longitudinal muscle passes directly down the intersphincteric space and then splits into many septa which course between the bundles of the subcutaneous external sphincter to insert into the skin of the lower anal canal and adjacent perineum. The area enclosed by these septa is generally accepted as the perianal space, which is separate and medial to the ischiorectal space. Adherents to the concept of the intermuscular septum would call the area medial to the perianal space the submucous space, while those who believe in the mucosal suspensory ligament of Parks would site the marginal space between the two aforementioned spaces. Yet more differences surround descriptions of the 'corrugator cutis ani' whose nature (and even existence) have been disputed (*Table 2*) since it was first described in 1878 by Ellis as a thin stratum of smooth muscle fibres radiating out under the perianal skin, superficial to the subcutaneous external sphincter[28].

## Purpose of the longitudinal muscle

A review of the literature concerning the anatomy of the conjoined longitudinal muscle reveals little uniformity in description. Despite this, roles for it in both health and disease have been postulated. Connections with structures outside the anal sphincter complex and intimate ramifications within the complex point to its role in fixing the anorectum to the pelvis[4]. Shafik[6] considers the muscle to have only a minimal role in continence, potentiating the action of the base loop in maintaining an airtight anal seal The most important role of the muscle is in contraction during defaecation, which leads to shortening and widening of the anal canal and eversion of the anal orifice Shafik[6] suggests that its name should describe its action and proposes the descriptive term 'evertor ani muscle' *In vitro* studies also indicate a possible role in defaecation[1]. Shearing forces from straining at stools, combined with the degenerative effects of ageing, have led Haas and Fox[19] to implicate the structure in the pathogenesis of haemorrhoids and prolapse, and imply that, by virtue of the meshwork to which the longitudinal muscle contributes, surgical division of the sphincters may lead to less deterioration in function than might otherwise be expected. Extensions ramifying from the intersphincteric plane are used to divide the adjacent tissues into named spaces and so are deemed important in the containment of sepsis. The same structures are also implicated as the pathways along which sepsis may spread and the course of fistula tracks.

## Conclusion

Despite an explosion of interest in anorectal physiology in the past decade it is surprising that there remains an anal canal muscle, the anatomy of which is uncertain and the function of which unknown Perhaps another step forward in our understanding of pelvic floor disorders must await suitable methods of determining its function in the living.

## Acknowledgements

The authors thank Mr N L Webb for drawing *Figures 1–4*

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Paper accepted 26 March 1992

# Digests

**Der Chirurg**

Zeitschrift für alle Gebiete der operativen Medizin

Organ des Berufsverbandes der Deutschen Chirurgen e V
Organ der Deutschen Gesellschaft für Chirurgie

**Br. J. Surg. 1992, Vol. 79,
September, 885–887**

*Continuing our exchange with* Der Chirurg, *Professor Christian Herfarth and Dr Thomas Lehnert have this month selected key papers from the April to June issues of that journal. Comments specific to the content of their digest should be sent to the address given, although* The British Journal of Surgery *would be glad to receive a copy.*

## Laparoscopic surgery

In April the annual meeting of the German Surgical Society was held at its traditional venue in Munich. One of the meeting's major issues was laparoscopic surgery, which was covered by a number of papers in the April congress issue of *Der Chirurg*.

In a prospective randomized study from Ulm, laparoscopic cholecystectomy was compared with 'mini-lap' cholecystectomy[1]. Mini-lap cholecystectomy was defined as that in which the length of the abdominal incision did not exceed 50 per cent of the distance between the skin level and the junction of cystic and hepatic duct. Exclusion criteria were suspected malignancy, liver cirrhosis with portal hypertension, acute cholecystitis, gallbladder empyema, choledocholithiasis, previous upper abdominal surgery and obesity exceeding 30 per cent on the Broca index During the study period of October 1990 to October 1991 a total of 325 patients underwent elective cholecystectomy. Seventy-seven patients were eligible for the study and gave informed consent to participate (24 per cent). Endpoints were mortality, morbidity, length of operation and hospital stay, respiratory function, postoperative pain and consumption of analgesics.

Forty patients were randomized to laparoscopic cholecystectomy and 37 to the mini-lap procedure. There were no postoperative deaths. One patient in each group had a serious complication: bleeding after laparoscopic cholecystectomy and bile duct injury during mini-lap cholecystectomy. Operative times were similar with a mean of 101 min for both procedures. The mean(s.e.m.) postoperative hospital stay was 3·5(1·2) days for laparoscopic cholecystectomy *versus* 5·8(3·5) days for mini-lap cholecystectomy ($P < 0{\cdot}001$). Evaluation of respiratory function revealed that preoperative vital capacity was comparable for both groups, but on days 1–3 after operation was significantly better for patients undergoing laparoscopic cholecystectomy ($P < 0{\cdot}01$). No difference in pulmonary function was found when forced expiration volumes were compared (75 per cent before operation for both groups; 73–82 per cent afterwards for laparoscopic treatment *versus* 72–75 per cent for mini-lap). The postoperative need for analgesia was less in patients treated laparoscopically, although not significantly so. Subjective assessment of pain using a visual scale revealed that patients experienced significantly less discomfort following laparoscopic cholecystectomy when coughing, getting up from bed and even in a recumbent position. The authors conclude that laparoscopic cholecystectomy is better in terms of postoperative pulmonary function and this was related to reduction of postoperative pain. Whether this difference would persist if patients with mini-lap cholecystectomy had wound incisions infiltrated with local anaesthetic at the end of the operation as has been described earlier remains unknown.

The limits of laparoscopic surgery have yet to be defined. The group from Ludwigshafen[2] reported treatment of a patient in whom cholecystectomy and sigmoid resection were performed laparoscopically during the same operation. Resection of the colon was indicated for two sigmoid polyps with grade 2–3 dysplasia on endoscopic biopsy and which could not be removed endoscopically. Technically the authors used a reversed Trendelenburg position for resection of the sigmoid colon. The superior rectal artery and vein were divided using an Endo-GIA stapler (US Surgical, Norwalk, Connecticut, USA). The lumen of the colon was closed with an externally tied ligature distal to the polyps, the rectum transected approximately 4 cm proximal to the peritoneal fold and the colon exteriorized transanally. A second ligature was placed around the sigmoid colon proximal to the polyps. Following transection of the proximal colon it was removed transanally. Purse-string sutures were then placed around the proximal colon and the rectal stump and a circular stapler introduced transrectally to complete the anastomosis. Intraoperative rectoscopy and a water immersion test documented completeness of the anastomosis. The postoperative course was uneventful, but histological examination of the specimen revealed $pT_2N_0M_0–G_1$ carcinoma with none of 15 lymph nodes showing tumour infiltration.

In a paper from Erlangen and Suhl[3] the initial clinical experience with laparoscopic abdominoperineal excision of the rectum for rectal cancer is described. The inferior mesenteric artery and vein were divided using an Endo-GIA stapler. The same instrument was used for transection of the colon. Laparoscopic mobilization of the rectum was similar to the conventional technique with anterior and posterior dissection followed by dissection of the lateral tissue planes down to the level of the levator muscles. Colostomy was accomplished by pulling the mobilized proximal colon (after closure with staples) through an incision via which one of the two left-sided trocars (20 mm) had been introduced. At the time of report the authors had treated four patients with operative times ranging from 4 h 30 min to 6 h 30 min.

Although colonic resection and standard lymphadenectomy is technically feasible laparoscopically, the technical difficulties of such an approach should not be underestimated. Randomized trials and several years of follow-up are required before the value of laparoscopic surgery for malignant disease can be established.

Two reports deal with laparoscopic treatment of inguinal hernia. Surgeons in Göttingen[4] treated 35 patients for direct ($n = 3$) and indirect ($n = 32$) inguinal hernia. The technique includes mobilization of the hernial sac so that it can be drawn from the inguinal canal into the peritoneal cavity. A 2–3-cm incision is made at the base of the sac. The inguinal canal is occluded by insertion of Marlex mesh (C. R. Bard, Massachusetts, USA) rolls (Marlex mesh 4–5 cm long rolled up to a diameter of approximately 8 mm and secured by several circular ties). The internal inguinal ring is covered with two to three pieces of mesh 4 × 4 cm and the peritoneum closed over the mesh with clips. One patient developed a haematoma Patients left hospital after a mean of 4·2 days (conventional herniorrhaphy 10·2 days) and returned to work after 3·3 weeks (conventional 5·2 weeks). Evaluation of pain scores showed that the method caused less discomfort during the first 6 weeks.

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Ultrasonographic studies indicated that none of the implants was dislocated.

Work from Olpe[5] describes an alternative laparoscopic approach applied to patients with indirect ($n = 71$) and direct ($n = 33$) hernias. For indirect hernias a small skin incision is made over the inguinal ligament. Through this incision a long non-absorbable suture is brought into the peritoneal cavity under laparoscopic control medially to the epigastric vessels through the inguinal ligament, through the hernial sac and through the posterior wall of the inguinal canal From there the suture is brought out through the laparoscopic canal and tied together with another suture that has been advanced via the same route 3–5 mm beside the first. Both sutures are then pulled back into the peritoneal cavity and tied exteriorly over the externus aponeurosis. Two additional pairs of sutures are placed laterally to the epigastric vessels in the same fashion and serve to occlude the inguinal canal together with the hernial sac. For direct hernias the tuberculum pubicum, the inguinal ligament and Cooper's ligament are all visualized laparoscopically after incision of the peritoneum. Again small skin incisions are made and straight and curved awls are used to advance and tie non-absorbable sutures in the same manner as for indirect hernias. For the direct hernia, however, the sutures are placed through the medial and lateral aspect of the internal hernial opening Three to four suture pairs were used for direct hernia closure.

The mean operative time was 30 min. Two patients experienced bleeding from the laparoscopic access requiring suture haemostasis; three developed suture granulomas. The length of hospital stay was 4 days on average and was influenced by associated diseases. No patient developed signs of testicular ischaemia, hydrocele or inguinal nerve irritation During the short follow-up period two male patients had direct inguinal hernia recurrence that required Shouldice repair.

An invited commentary by Schumpelick[6] concludes that the temptation to apply laparoscopic techniques should perhaps be more restrained. The introduction of alloplastic material into the inguinal canal may cause unforeseeable problems and the method does little to strengthen the posterior wall of the inguinal canal

## Prophylaxis of venous thrombosis

In the past decade *The British Journal of Surgery* has published a number of prospective randomized trials studying the efficacy of various regimens in preventing postoperative venous thrombosis. The extent to which such trials have influenced clinical practice is not clear. A national survey conducted in Germany therefore attempted to determine current clinical practice for prophylaxis of postoperative venous thromboembolism[7]. Questionnaires were sent to surgical units of 940 hospitals in the then West Germany and 564 evaluable questionnaires (60 per cent) covering a total of 1 200 000 operations were returned. Virtually all units used physical methods to prevent postoperative thromboembolism. All relied on early postoperative mobilization of the patient and 92 per cent used compression stockings. The use of in-bed 'bicycles' was reported by 20 per cent of surgical departments. Pneumatic calf compression was used by only 2 per cent.

All answering institutions used heparin as medical prophylaxis in addition to physical measures. Unfractionated heparin alone was used by 48 per cent of departments and 9 per cent used low molecular weight heparin alone. Combinations of both or with dihydroergotamine–heparin or other combinations were used by 43 per cent of units; 81 per cent used heparin prophylaxis for all patients and in 19 per cent of units such prophylactic treatment was restricted to patients at risk

Medical treatment was administered for 3–8 days by 36 per cent of units, for 9–16 days by 17 per cent, until full mobilization of the patient by 31 per cent and until discharge by 16 per cent

Surgical units were also asked to indicate the number of venous thromboses and episodes of pulmonary embolism during the observation period. Deep venous thrombosis was reported in 5965 patients for an incidence of 0·5 (range 0·4–0·9) per cent and pulmonary embolism was reported in 2557 patients (0·2 (range 0·2–0·3) per cent). The incidence of such complications was lower in patients treated in general or vascular surgical units (0·3 per cent) compared with those treated in orthopaedic or trauma units (0 8 per cent) ($P < 0{\cdot}0001$). No significant differences were established regarding the duration of heparin treatment and no significant differences could be elicited with regard to venous thrombosis or pulmonary embolism when the different types of heparin (unfractionated *versus* low molecular weight) or doses of unfractionated heparin (5000 units twice or three times daily) were considered

## Breast cancer

In 1983 the German Breast Cancer Study Group[8] initiated a multicentre prospective randomized trial to compare mastectomy with breast-preserving therapy for small carcinoma of the breast ($pT_1\,N_0\,M_0$). After tumour removal and diagnostic axillary dissection, patients were to be randomized to formal mastectomy or radiotherapy (50–60 Gy, 6–7 weeks) with preservation of the breast. Between 1983 and 1989 a total of 1119 patients were admitted to the study but, following publication of the results from the NSABP B-06 protocol, randomization dropped and only 72 patients (6 per cent) consented to randomization. The randomized study had to be abandoned and the trial was continued as a prospective observation study. Endpoints were recurrence-free and overall survival

According to the patients' treatment preference, 303 patients were treated by mastectomy and 733 had breast-preserving treatment including radiation therapy Patients in the mastectomy group were older and more were postmenopausal. Differences in tumour size, oestrogen receptor status and progesterone receptor status between both groups were small, whereas tumour grading and histological types were almost identical in the two groups. The mean length of the observation period was 48 months in both groups For statistical analysis the log rank test and the Cox regression model were used.

In a univariate analysis tumour grading and size were determined as prognostic parameters, while age, receptor status and histological type had little effect on disease-free survival. Resection margins influenced disease-free survival only in as much as disease-free survival of patients with 'uncertain' margins was 62 per cent at 5 years compared with at least 80 per cent for patients with clear margins. The extent of clear margins (0–2 mm, 3–5 mm or >5 mm) did not significantly influence the disease-free survival rate.

A multivariate analysis accounting for confounding factors such as tumour size and grading, and age of the patients, revealed no significant differences between breast-preserving treatment or mastectomy ($P = 0{\cdot}21$), but confirmed the prognostic significance of tumour size ($P = 0{\cdot}037$) and grade ($P = 0{\cdot}03$). Pending further analysis of subgroups this prospective observation study does not reveal any significant advantages of mastectomy for patients with $pT_1\,N_0\,M_0$ tumours of the breast

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*In the third of our quarterly exchange of digests, Dr Hiram Polk, Editor of* The American Journal of Surgery, *has this month highlighted papers from the April, May and June issues of that journal. A digest of the same months'* British Journal of Surgery *prepared by our Editor, Professor John Farndon, appears in the September issue of the American journal. Dr Polk's address for correspondence is given at the end of his summary.*

## Trauma

Recent contributions to *The American Journal of Surgery* have reflected the broader dimension of current surgical practice in a rather pointed fashion. Thoracotomy in the dying trauma victim has often been characterized as a 'prelude to death' and as futile (and even less warmly) by others. Maier and associates, from a trauma centre in the Pacific north-west, found that 'resuscitative thoracotomy' was futile in patients who had sustained blunt trauma, but did save the lives of three of eight victims with penetrating injury[1]. Importantly, they described another 54 patients who underwent urgent but non-resuscitative thoracotomy for trauma, of whom 40 recovered. Thoracotomy in dire situations will save the lives of some victims with penetrating trauma.

## Pancreatic surgery

To stent or not to stent pancreatic or biliary anastomoses is a continuing clinical surgical controversy on which little light has been shed in recent years. Biehl and Traverso studied 34 anastomoses between the pancreas and a Roux limb in dogs and concluded that stented anastomoses were less likely to leak and/or stenose than unstented ones but none of the observations was statistically significant[2]. Score a half-point for the stenters.

## Oncology

The idea that some tumours not amenable to direct surgical attack may yield to other innovative treatments is an old one. The concept of deliberate embolization combined with delivery of specific drugs to the tumour site has been addressed in two recent reports. Bismuth and colleagues treated 291 patients with hepatocellular cancer by chemoembolization with ethiodized oil, doxorubicin, and a gelatin sponge[3]. Not surprisingly, early mortality was related to hepatic functional reserve but the rate was only 7 per cent in non-cirrhotic patients in the first 60 days. Fifty-five per cent of patients had no change in the size of tumour. Forty-three of the 291 underwent hepatic resection and/or transplantation after chemoembolization if there had been significant necrosis or diminution in size of the tumour. The authors concluded that the treatment as preoperative therapy was associated with increased survival compared with historical controls.

Fletcher and co-workers treated patients with metastatic carcinoids by a combination of chemoembolization with 5-fluorouracil and systemic chronic octreotide acetate[4]. They noted that all eight patients were symptomatically improved and alive, although the mean follow-up for a generally slowly progressive tumour was only 22 months after chemoembolization.

Liver transplantation techniques continue to facilitate the direct attack on hepatic tumours. Huguet and colleagues from Monaco describe and illustrate some very specific techniques that are especially useful for lesions that, by virtue of their proximity to major hepatic veins on the inferior vena cava, have traditionally been considered irresectable[5].

## Colorectal surgery

Ames and colleagues from the M. D. Anderson Cancer Center in Houston, Texas, reassessed the old issue of extended resection for selected colorectal cancers that present with extension beyond the levels of standard resection[6]. Their series of 101 patients included a high proportion (46 patients) with urinary tract involvement. They found that intravenous pyelography, abdominal computed tomography and cystoscopy helped define the extent of malignant invasion. They demonstrated significant survival in patients subjected to an extended curative resection (54 per cent actuarial 5-year survival rate). This experienced group stressed the value of preoperative assessment and strategic planning for operation in this important subset of patients with colorectal cancer.

For the first time in the USA, national data are available on outcomes in a large unselected series of patients from the Medicare data banks (patients >65 years of age). While these reports have little or no surgical input into their preparation, the raw data are reassuring as to the high standard of care for the average elderly American. Whittle *et al.*[7] examined data on 5586 patients with colonic cancer treated between 1983 and

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1985. The hospital mortality rate was 5 per cent, ranging from 3·3 per cent in the youngest beneficiaries (i.e. 66–69 years of age) to 9·3 per cent in those >85 years old; men had a slightly higher perioperative death rate. The survival rate irrespective of cause of death or cancer status was 63 per cent at 2 years, an especially interesting figure since the population included all patients undergoing resection, regardless of whether this was palliative or curative. Such data are important because they supplement previous reports, which have tended to be from individuals and institutions with special interests or skills in the care of a given illness.

## Gastro-oesophageal surgery

Less invasive forms of surgical therapy continue to proliferate internationally and occupy much of contemporary surgical debates and publications. No BJS reader will be surprised to learn of Cuschieri and associates' description of the successful laparoscopic repair of large hiatal hernias[8]. The important long-term evolution will clarify whether these methods can compete with the 'gold standard' of transabdominal fundoplication, i.e. <1 per cent hospital mortality rate and a 96 per cent long-term cure rate for reflux oesophagitis. The laparoscopists will have to be pretty good

Rakic and colleagues from Belgrade describe an uncommon but physiologically significant disease associated with hiatal hernia and reflux oesophagitis[9]. The healing of a gastric ulcer after reduction and cure of a paraoesophageal hiatal hernia is directly related to the tendency of fundoplication wraps (left in the chest when a very short oesophagus complicates a sliding hiatal hernia) to develop gastric ulcers. A mechanical cause for such ulceration was assumed which the Belgrade group confirms The fundal wrap left in the chest has been abandoned when oesophageal shortening is severe. The confirmation of an editor's prejudices is always well received.

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*The following five papers were presented at the 75th meeting of the Surgical Research Society, with Professor N. Browse in the chair. The meeting was held on 9–10 January 1992 at The Royal College of Surgeons of England.*

# Assessment of stripping the long saphenous vein in the treatment of primary varicose veins

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*Stripping of the long saphenous vein (LSV) may prevent recurrence of varices, although this has not been demonstrated using objective criteria. The aim of this study was to determine whether the addition of LSV stripping, from groin to upper calf, to saphenofemoral junction (SFJ) ligation prevents residual reflux, and whether LSV stripping to the upper calf results in greater neurological complications. Sixty-nine patients with primary varicose veins, LSV reflux and SFJ incompetence, confirmed by duplex ultrasonography and photoplethysmography, were studied. A total of 105 limbs were treated by SFJ ligation and avulsion of varices; patients were randomized to undergo stripping of the LSV to the upper calf* ($n = 49$) *or no additional treatment* ($n = 56$)*. Three months after surgery all patients were examined clinically, by duplex ultrasonography and by photoplethysmographic tests of venous function, to establish the extent of persisting varices. Fewer persisting incompetent LSVs in the calf were found when the LSV was stripped* ($n = 9$) *than after SFJ ligation alone* ($n = 25$) ($P < 0{\cdot}01$)*. Photoplethysmographic refilling times were improved to a similar extent in both groups after surgery but were lower in those who had residual LSV reflux* ($P < 0{\cdot}05$)*. Six limbs developed paraesthesia in the distribution of the saphenous nerve: two in the group that were stripped and four in those that were not. These data suggest that LSV reflux is more completely abolished by combining LSV stripping with SFJ ligation; stripping the LSV to the upper calf does not result in a higher incidence of injury to the saphenous nerve.*

Reported rates of recurrence of disease after treatment of superficial varicose veins range from 7 to 65 per cent[1,2]. The reasons for this variation are numerous. lack of a suitable definition of recurrence, inadequate length of follow-up, progression of the disease process, inaccurate initial diagnosis, operative procedures undertaken with few controlled trials, and the ill-defined 'surgeon-related variables' No report has so far been published in which the results have been judged using objective criteria The results of the studies cited above were assessed by clinical means; it is hardly surprising that the surgeon who performed the procedure should find a satisfactory outcome[1].

Numerous studies have attempted to identify reasons for this high recurrence rate. The most common cause cited is an inadequate initial operation with failure to perform a flush saphenofemoral ligation[1,3–7]. Failure to identify and treat other sources of reflux, such as saphenopopliteal or mid-thigh perforating veins, is also common[3,8]. Considerable controversy exists over the need to strip the long saphenous vein (LSV). Proponents argue that stripping produces a better immediate result and a lower long-term recurrence rate[9–11]. However, this must be weighed against the greater morbidity associated with stripping the vein, owing to bleeding, pain and wound infection, which may result in a longer hospital stay More importantly, after stripping there is an increased incidence of injury to the saphenous nerve[11–13]. Finally, stripping the LSV results in the loss of a possible conduit suitable for arterial or venous reconstruction.

It has been suggested that the incidence of injury to the saphenous nerve may be reduced if the LSV is stripped from the groin to the upper calf alone[13,14]. The saphenous nerve is closely related to the LSV only in the lower calf[15], therefore stripping the LSV only in the thigh should reduce the incidence of injury to the nerve while ensuring that potential perforating vessels (e.g. mid-thigh and tibial tubercle perforating veins) are avulsed[16]. Negus reviewed an uncontrolled, retrospective series of 71 patients a mean of 3 7 years after such a procedure and found a 13 per cent recurrence rate and a 4 per cent incidence

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**Table 1** *Controlled clinical trials comparing the results of saphenofemoral ligation with and without stripping of the long saphenous vein*

| | | | | | | LSV stripping | | | No LSV stripping | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Reference | Year | Design | No. of patients | Follow-up (months) | Assessment | No of limbs | Recurrence (%) | Paraesthesia (%) | No of limbs | Recurrence (%) | Paraesthesia (%) |
| McElwee and Maisel[17] | 1947 | Retrospective | 288 | 18 | Clinical | 104 | 19 | – | 121 | 12 | – |
| Mathiesen[18] | 1953 | Retrospective | 232 | 44 | Clinical | 53 | 24 | – | 179 | 35 | – |
| Lofgren *et al.*[9] | 1958 | Retrospective | 400 | 60 | Clinical | 81 | 6 | – | 101 | 60 | – |
| Rintoul and MacPherson[19] | 1975 | ?Prospective, not randomized | 325 | >60 | Patient/ clinical | 70 | 1–24 | – | 352 | 14–33 | – |
| Jakobsen[10] | 1979 | Prospective, randomized | 326 | 36 | Clinical | 161 | 10·2 | – | 165 | 34·8 | – |
| Munn *et al*[11] | 1981 | Prospective, blind, randomized | 100 | 30–42 | Clinical | 57 | 36 | 33 | 57 | 60 | 14 |
| Woodyer and Dormandy[20] | 1986 | Prospective, randomized | 200 | 36 | Patient/ clinical | – | – | – | – | – | – |
| Hammarsten *et al*[21] | 1990 | Prospective, randomized | 42 | 52 | Clinical, SGP | 24 | 12 | – | 18 | 11 | – |

LSV, long saphenous vein; SGP, strain-gauge plethysmography; –, not documented in paper

of neurological symptoms in the distribution of the saphenous nerve[13].

There are few controlled trials comparing the results of saphenofemoral junction (SFJ) ligation alone with those of SFJ ligation with stripping of the LSV (*Table 1*). Most series are retrospective and all have relied on patient or clinical assessment of improvement. McAdam *et al.*[22] showed that these criteria are far from precise, reporting an intraobserver agreement comparing symptomatic response and visual improvement of only 30 per cent. Furthermore, in evaluating visual changes in the affected limb, interobserver agreement was only 60 per cent. In the same study the operating surgeon found residual varices in 58 per cent of patients, yet 64 per cent of the patients themselves claimed to be 'perfectly satisfied' with the results of operation. Neither the patient nor the surgeon appear to be reliable assessors of improvement following surgery. Both are prejudiced by preconceived standards that appear to vary within each observer and are also different between them. Subjective improvements are inadequate criteria to judge the results of varicose vein surgery.

Modern vascular laboratory techniques allow non-invasive, objective, repeatable measurements in the assessment of venous disease. The aim of this study was to compare the benefit of SFJ ligation and stripping the LSV to the upper calf with that of SFJ ligation alone in the treatment of primary varicose veins from SFJ reflux. Patients were investigated in a randomized study by objective vascular laboratory tests carried out by an observer unaware of the nature of the surgical treatment. Such stringent criteria have not previously been applied to this problem.

## Patients and methods

A total of 69 patients of median age 50 (interquartile range (i.q.r.) 41–62) years attending the vascular laboratory for preoperative assessment were entered into the study. All limbs had primary varicose veins in the distribution of the LSV and were confirmed to have only SFJ incompetence by duplex ultrasonography. All patients gave informed consent to the study.

Before operation patients answered a questionnaire in which they graded the symptoms of 'itching' and 'aching' in each affected limb on a scale of 0 to 10, 0 representing no itch or ache and 10 the worst they could imagine. They were also assessed clinically for the presence of paraesthesia in the distribution of the saphenous nerve. Photoplethysmography was used for functional assessment of the venous system; 95 per cent photoplethysmographic refilling times were determined in the dependent legs of the sitting patient after ten dorsiflexions of the ankle. In this laboratory[23] normal venous refilling time is $\geqslant 15$ s. Duplex ultrasonography (Acuson 128; Acuson, Mountain View, California, USA) using a 7-MHz linear array transducer was undertaken with the patient standing on the leg opposite to that being examined. Both the deep and superficial veins were assessed to identify sites of venous incompetence. Reflux was defined as reverse flow lasting $>0{\cdot}5$ s after the release of manual calf compression. Reflux at the SFJ and the LSV was confirmed and the LSV examined along the length of the thigh to detect any perforating vessels.

All patients were admitted under the care of one surgical team. At the time of operation, they were randomized to either SFJ ligation and multiple avulsions or to SFJ ligation, stripping of the LSV to below the knee and multiple avulsions. Neither the patient nor the vascular laboratory staff were told of the operative allocation. All operations were undertaken by experienced surgeons. After operation, elastic compression stockings were worn until the patient attended the outpatient department for removal of sutures 7–10 days later. Wounds were inspected for evidence of erythema and serous or purulent discharge, which were taken to signify wound infection. Any complications such as excessive haemorrhage or haematoma were also noted.

Venous assessment was repeated in all patients 3 months after surgery. They were required to grade the degree of aching and itching in each limb as before. They were examined for paraesthesia in the distribution of the long saphenous nerve and all underwent duplex ultrasonography and photoplethysmography. On duplex scanning particular attention was paid to the effectiveness of SFJ ligation and to the presence of residual reflux in the LSV at calf level.

The patient randomization code was revealed at the end of the study and a comparison made between the improvement in symptoms, photoplethysmographic refilling times and residual reflux on duplex ultrasonography in the two groups. The Statistical Package for the Social Sciences (SPSS, Chicago, Illinois, USA) was used to analyse the data using non-parametric tests: paired (Wilcoxon signed rank test) for within-subject variation and unpaired (Mann–Whitney *U* test) for between-subject variation. Results are given as median (i.q.r.).

## Results

A total of 56 limbs in 36 patients were randomized to SFJ ligation and 49 limbs in 33 patients to SFJ ligation and LSV stripping. *Table 2* shows the age distribution, sex ratio, duplex scan findings, photoplethysmographic refilling times and symptoms in the two groups. Although the patients who underwent LSV stripping in addition to SFJ ligation were younger than those who had SFJ ligation alone, neither this nor any of the other factors measured was significantly different between the two groups (Mann–Whitney *U* test).

All patients underwent the allocated procedure and all attended for assessment after operation. No patient had a haematoma; there were two cases of minor serous wound discharge, one at the lower site of the incision required to strip the LSV and the other at the groin incision in a patient who underwent SFJ ligation only. *Table 3* shows the results of duplex ultrasonography, photoplethysmography and clinical examination in the two groups. On duplex scanning the SFJ appeared to be intact in one limb. This limb was excluded from further analysis. There was a significantly higher incidence of residual reflux in the LSV in the group that had undergone SFJ ligation alone ($\chi^2 = 7{\cdot}5$, $P < 0{\cdot}01$). The 95 per cent refilling times were not different between the groups (Mann–Whitney *U* test); the incidence of paraesthesia along the distribution of

**Table 2** *Results before randomization to saphenofemoral junction ligation alone or with the addition of long saphenous vein stripping in 105 limbs*

| | SFJ ligation only | SFJ ligation and LSV stripping |
|---|---|---|
| No. of limbs | 56 | 49 |
| No. of patients | 36 | 33 |
| Sex ratio (M:F) | 9:27 | 10:23 |
| Age (years)* | 53 (46–68) | 43 (39–54) |
| Duplex ultrasonography | | |
| SFJ reflux | 56 | 49 |
| LSV reflux | 56 | 49 |
| Mid-thigh perforators | 8 | 9 |
| Photoplethysmography | | |
| 95% refilling time (s)* | 11 (7–16) | 12 (8–16) |
| Clinical assessment | | |
| Grade of ache in limb* | 4 (3–6) | 3 (0–5) |
| Grade of itch in limb* | 0 (0–4) | 1 (0–3) |
| No. with paraesthesia | 0 | 0 |

*Values are median (interquartile range). SFJ, saphenofemoral junction; LSV, long saphenous vein

**Table 3** *Results after operation in the groups undergoing saphenofemoral junction ligation alone or with the addition of long saphenous vein stripping*

| | SFJ ligation only | SFJ ligation and LSV stripping |
|---|---|---|
| No. of limbs | 56 | 49 |
| Duplex ultrasonography | | |
| Residual SFJ reflux | 1* | 0 |
| Residual LSV reflux | 25 + 1* | 9† |
| Residual thigh perforators | 6 | 2 |
| Photoplethysmography‡ | | |
| 95% refilling time (s) | 18 (13–25) | 21 (15–28) |
| Clinical assessment | | |
| Paraesthesia | 4 | 2 |
| Haematoma | 0 | 0 |
| Wound infection | 1 | 1 |

‡Values are median (interquartile range). SFJ, saphenofemoral junction; LSV, long saphenous vein. *One limb in which residual LSV reflux was caused by inadequate SFJ ligation. †Yates' $\chi^2 = 7{\cdot}5$, $P < 0{\cdot}01$

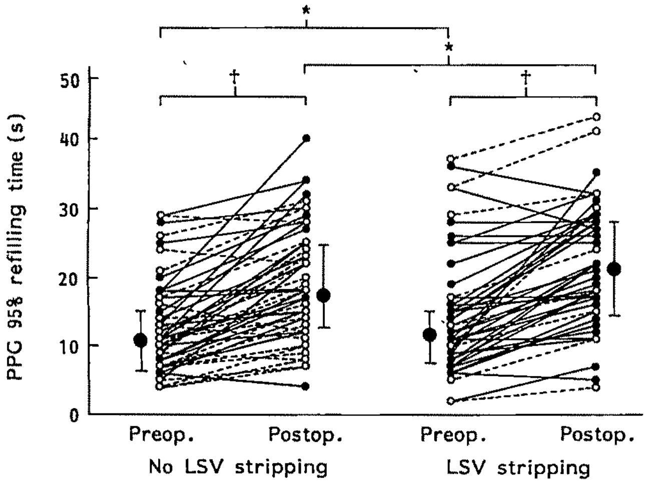

**Figure 1** *Comparison of preoperative and postoperative photoplethysmography (PPG) refilling times in limbs that underwent saphenofemoral junction ligation alone with those in limbs that had long saphenous vein (LSV) stripping in addition.* ○, *Postoperative reflux,* ●, *no postoperative reflux. Bars are median (interquartile range).* *P *not significant (Mann–Whitney* U *test);* †P < 0·001 *(Wilcoxon signed rank test)*

the saphenous nerve was 7 per cent in the group that had SFJ ligation alone compared with 4 per cent in patients undergoing additional LSV stripping.

*Figure 1* shows the preoperative and postoperative photoplethysmography results in more detail to allow comparison between the two groups. In both the group that had SFJ ligation alone and in that which had additional LSV stripping, the 95 per cent refilling time was significantly improved following the procedure (Wilcoxon signed rank test for paired samples).

*Figure 2* compares the preoperative and postoperative 95 per cent refilling times between the limbs that had residual LSV reflux and those that did not. Refilling times before operation were similar in both groups and improved following operation. However, those limbs that had residual LSV reflux had significantly lower postoperative refilling times ($P < 0{\cdot}05$, Mann–Whitney *U* test).

Finally, in the limbs that had LSV stripping in addition to SFJ ligation, there was a significantly greater improvement in the patients' subjective sensation of 'ache'; although 'itching' was reduced in both groups, there was no significant difference between them in this respect (*Figure 3*). The extent of

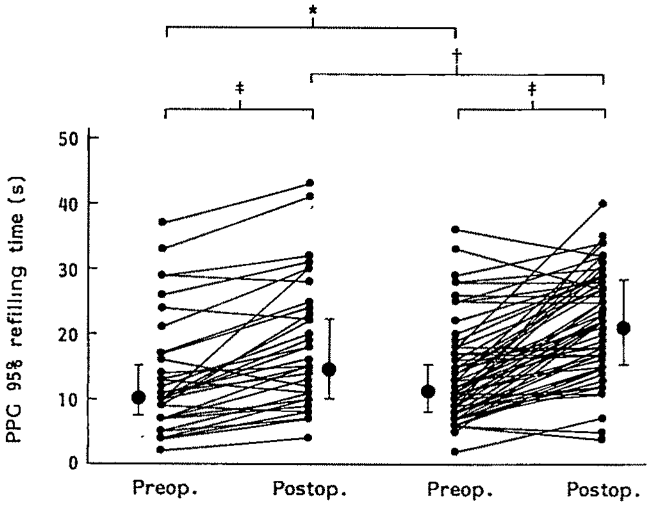

**Figure 2** *Comparison of preoperative and postoperative photoplethysmography (PPG) refilling times in limbs that had residual long saphenous vein reflux with those in limbs that did not. Bars are median (interquartile range).* *P *not significant,* †P < 0·05 *(both Mann–Whitney* U *test);* ‡P < 0·001 *(Wilcoxon signed rank test)*

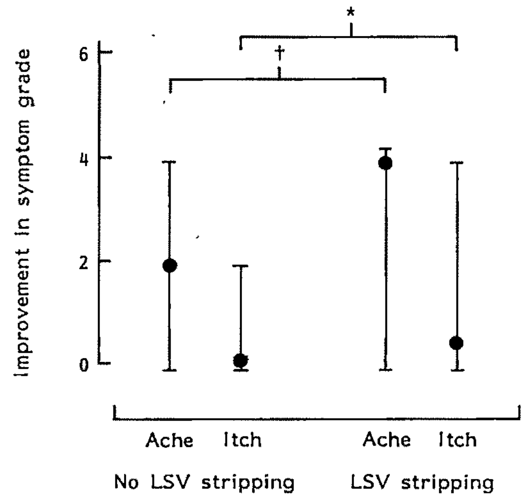

**Figure 3** *Improvement in the symptoms of 'aching' and 'itching' in limbs that had saphenofemoral junction ligation alone and in those that had long saphenous vein (LSV) stripping in addition. Values are median (interquartile range).* *P *not significant,* †P < 0·05 *(both Mann–Whitney* U *test)*

improvement was calculated by subtracting the postoperative from the preoperative grades (scale 0–10) as assessed by the patient. A positive value indicated improvement and a negative one a worsening of the symptom.

## Discussion

The failure to ligate one of the 105 SFJs underlines the apparent ease with which a surgeon can be misled by the variable venous anatomy at this site. This operation is often left to junior surgeons to perform and, not surprisingly, SFJ ligation error is the commonest cause of 'recurrence'[1,3–8]. A generous incision close to the inguinal ligament followed by meticulous dissection with visualization of all four quadrants of the SFJ is the only reliable way to avoid an inadequate operation[24,25].

In the group that underwent SFJ ligation only, 45 per cent of the LSVs in the calf had residual reflux. In contrast, in the group in which the LSV was stripped in addition to SFJ ligation, only 18 per cent of the LSVs in the calf had reflux on duplex ultrasonography. There was a significant improvement in refilling times in both groups but no difference in postoperative refilling times between the two groups, despite a difference in numbers with residual reflux. We suggest that this is the result of the small number of patients available for study. When the photoplethysmographic refilling times of those limbs with residual reflux in the LSV were compared with times for those without, the limbs without residual reflux had significantly longer refilling times (*Figure 2*). It is likely that with larger numbers the differences between the functional improvement as measured by photoplethysmography between those patients who had undergone LSV stripping and those who had not would become apparent.

McMullin *et al.* demonstrated that reflux in the LSV following SFJ ligation was associated with a lack of improvement in photoplethysmographic refilling time, which in turn was associated with a poorer subjective improvement as assessed by the patient[26]. This relationship is not absolute and, in common with their study, we found that in some 16 limbs with residual reflux on duplex scanning the refilling times had been normalized (>15 s); it may be that the amount of reflux was not sufficient to influence refilling times in these limbs. Nevertheless, it is apparent that residual reflux on duplex ultrasonography is associated with shorter photoplethysmographic refilling times and a worse subjective outcome. Although the circumstantial evidence is strong, it remains to be demonstrated whether residual reflux and a poorer functional outcome are associated with recurrent varicose veins in the longer term.

The source of reflux in the residual veins is unknown. In a few limbs, small-diameter tortuous vessels were noted to arise from the femoral vein at the site of SFJ ligation. Glass has recently proposed that recurrence of varicose veins may be the result of 'neovascularization' of the ligated LSV[27]. This may be true when the LSV is left *in situ*, but it does not explain the incidence of reflux when the LSV is stripped. Possibly, forward flow in the side branches of the vein under examination may, on entering the main vessel, flow retrogradely because of incompetent valves and be interpreted as reflux. Another explanation may lie in the presence or absence of perforating veins[8]. Before operation eight such vessels were identified in the group that did not have the LSV stripped and nine in those limbs where the LSV was stripped. After operation eight such veins were still present: six in those that had not had the LSV stripped and two where it had. All limbs that had residual thigh perforators also had residual reflux in the LSV at calf level. The apparent failure of LSV stripping to avulse the perforating vessels in two cases is because in one the perforator arose from a posterior branch of the LSV and in the other the LSV was stripped only as far as the knee, some 5 cm short of the tibial tubercle perforator. Also, ultrasonography of veins has shortcomings: we may have failed to identify other perforators and, because the resolution of such imaging is limited to vessels >2 mm in diameter, an unknown number of smaller perforating vessels may have been present. Certainly, any proposed mechanism to explain recurrent varicose veins must account for the difference in residual LSV reflux observed when the LSV is stripped compared with that when it is not.

The addition of stripping the LSV (to the upper calf) to the operative procedure of SFJ ligation and multiple avulsion of varicosities resulted in an improvement in the patients' subjective assessment of the symptoms of aching and itching. Neither procedure increased the incidence of wound haematoma, wound infection or paraesthesia along the distribution of the saphenous nerve.

The question of whether the LSV should be conserved for possible use as an arterial conduit needs to be addressed because autogenous vein grafts have a better long-term patency rate than prosthetic materials. Sutton and Darke, using peroperative saphenography in patients with primary varicose veins, found that 65 per cent of LSVs were not suitable for use as arterial grafts[16]. MacFarlane *et al.* have suggested that the lower part of the LSV is usually normal in patients with varicose veins, therefore stripping the LSV to the knee should preserve that part of the vein for possible future use[28]. Furthermore, Houser *et al.*, on reviewing 500 consecutive aortocoronary bypass procedures, found that in only 12 cases (2·4 per cent) was the LSV unsuitable for use because of either varicosities or previous stripping[29]. Stripping the LSV from the groin to below the knee would appear to be the most suitable compromise, leaving enough vein for possible future arterial surgery and yet dealing appropriately with the immediate problem of venous disease.

In conclusion, this study has shown that in a large proportion of cases SFJ ligation combined with multiple avulsion of varicosities fails to prevent venous reflux and fails to normalize venous function. In contrast, ligation of the SFJ and multiple avulsion of varicosities combined with stripping of the LSV to the upper calf results in fewer veins with residual reflux and a better functional outcome; such stripping does not increase the incidence of wound complications or paraesthesia along the distribution of the saphenous nerve.

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# Announcement

## Surgical Trainees Travel Award

Rhône-Poulenc Rorer is pleased to announce the winners of the first RPR Travel Award for Surgeons in Training, arranged in conjunction with the Association of Surgeons in Training (ASIT) and the British Orthopaedic Trainees Association. Mr Mark Proctor, Senior Registrar in Orthopaedics at The Royal London Hospital, has been awarded the first prize of £1500 for his essay on 'Non-union of the scaphoid: early and late management'. The second prize was awarded to Mr Adrian Casey, Registrar in Neurosurgery, Atkinson Morley's Hospital, London, who submitted an essay on 'Acute subdural haematomas'.

The awards will be presented at the ASIT Annual Dinner in Dublin on 23 September 1992 and the winning entries have been published in the ASIT 1992/1993 Year Book. Both winners will use the travel awards to visit training centres of excellence overseas that are relevant to their surgical specialties. The winners will be required to present a 10-min account of their trip at the ASIT AGM in 1993.

The Award has been devised to promote the exchange of information between surgical specialties in different countries and aims to encourage travel for education of trainees.

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# Duplex ultrasonography and pulse-generated run-off in selecting claudicants for femoropopliteal angioplasty

*Non-invasive assessment of lower limb vasculature may avoid unnecessary angiography in claudicants. Colour duplex ultrasonography of the femoral and popliteal arteries was performed to assess patency and the presence of any stenoses, and pulse-generated run-off (PGR) was used to assess the distal vasculature. In 65 legs colour duplex scanning was successful, compared with angiography, in identifying the site and type of disease in the femoropopliteal segment and 23 lesions were correctly identified as suitable for angioplasty. More patent distal vessels were demonstrated by PGR than by angiography; no vessels patent on angiography were missed by PGR. The estimated cost of diagnostic angiography was £330 per test compared with £52 for non-invasive assessment. By using duplex examination as a screening test, a potential saving of £8062 could have been made in this series. Duplex ultrasonography offers a non-invasive and cost-effective alternative to diagnostic angiography for clinically suspected infrainguinal arterial disease presenting as claudication. PGR was not of clinical value in assessing suitability for angioplasty.*

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Percutaneous angioplasty is often used in the treatment of patients with claudication secondary to disease of the superficial femoral and popliteal arteries. This has led to an increase in the number of patients undergoing angiography, even though open surgery may not be indicated[1–4]. Angiography has inherent risks, even when performed by the intravenous digital subtraction technique[5,6]. Non-invasive assessment of the lower limb and avoidance of angiography in those patients not suitable for angioplasty would be ideal. Furthermore, if patients suitable for angioplasty could be identified before angiography, better organization of radiology services might be achieved.

The development of colour duplex imaging has made this easier and findings from duplex ultrasonography have been shown to correlate well with the results of arteriography[7–12]. Below the tibioperoneal trunk duplex scanning is more difficult and, in an attempt to identify the patency of the distal run-off, the non-invasive technique of pulse-generated run-off (PGR) was used in this study Previous work has shown that preoperative measurement of PGR is a more accurate assessment of distal run-off than angiography in patients with critical ischaemia[12].

In this study the use of colour duplex scanning and PGR in assessing the distal vasculature of patients with clinically suspected infrainguinal disease that might be suitable for angioplasty is described.

## Patients and methods

A total of 52 patients, 13 women and 39 men, of median age 64 (range 56–80) years were studied. Six were diabetic, all had symptoms of intermittent claudication, which on clinical examination was thought to be due to superficial femoral artery disease suitable for angioplasty. Sixty-five limbs were investigated prospectively. Patients underwent initial investigation, with a recording of ankle:brachial pressure index before and after exercise to confirm ischaemia. An Ultramark 9 (Advanced Technology Laboratories, Stevenage, UK) colour duplex scanner with linear 5-MHz and phased array 2 25-MHz transducers was used to assess the femoral and popliteal arteries Scanning started at the common femoral artery and finished after attempted visualization of the branches of the popliteal artery. Patients then underwent PGR examination of the calf vessels[13] (*Figure 1*). All patients subsequently underwent biplanar intra-arterial angiography[14,15] within 2 weeks of the non-invasive studies The criteria for suitability for angioplasty were a patent origin of the superficial femoral artery that contained either a >50 per cent stenosis or an occlusion of <10 cm. The degree of stenosis on duplex examination was calculated by evaluating change in peak maximum systolic velocities[16]. An 'atheromatous' superficial femoral artery was defined as one that had changes in peak maximum velocity, but not to the extent necessary to be classified as having 50 per cent stenosis, with narrowing seen on B-mode ultrasonography. The results of all the tests were compared.

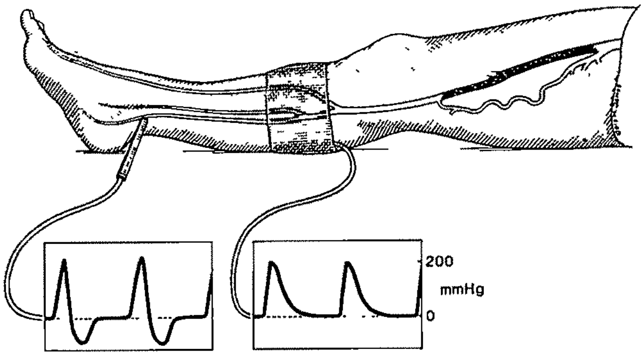

**Figure 1** *Pulse-generated run-off system with a calf compression cuff and Doppler insonation of a calf vessel*

## Results

All 23 limbs thought on duplex scanning to have a lesion suitable for angioplasty had the lesion confirmed by angiography. The latter did not identify any further limbs suitable for angioplasty. One patient died from retroperitoneal haemorrhage due to a dissection of an external iliac artery following diagnostic angiography, despite subsequent surgery. Duplex scanning and angiography are compared in *Table 1*. An occluded origin of the superficial femoral artery was seen

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**Table 1** *Duplex scanning compared with angiography in 65 limbs*

| Superficial femoral artery status | Sensitivity | Specificity | Positive predictive value | Negative predictive value | Accuracy |
|---|---|---|---|---|---|
| Occluded ($n = 28$) | 97 | 97 | 96 | 97 | 97 |
| Stenosed ($n = 17$) | 94 | 98 | 94 | 98 | 97 |
| Atheromatous ($n = 16$) | 100 | 100 | 100 | 100 | 100 |
| Disease-free ($n = 4$) | 100 | 100 | 100 | 100 | 100 |

Values are percentages

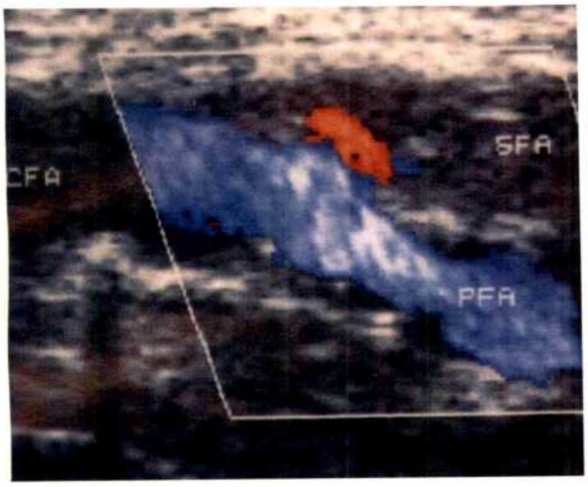

**Figure 2** *Colour duplex image, illustrating occlusion of the superficial femoral artery (SFA) origin. CFA, common femoral artery; PFA, profunda femoris artery*

in 15 limbs, which were therefore not suitable for angioplasty; 17 limbs had a stenosis suitable for angioplasty and six of the 28 limbs with an occlusive lesion had an occlusion $<10$ cm long which was dilated. *Figure 2* shows a typical example of an occlusion of the superficial femoral artery origin as seen on duplex scanning. In the four limbs with disease-free superficial femoral and popliteal arteries, the Doppler signal in the common femoral artery was monophasic and on angiography significant aortoiliac disease was seen. The cost of a duplex scan was estimated at £52, compared with £330 for an angiogram.

PGR and angiographic evaluation of run-off agreed in 54 limbs, however in 11 (17 per cent) PGR demonstrated better run-off than arteriography, a not unusual finding in the presence of ischaemia. The PGR examination did not help to define the suitability of a lesion for angioplasty.

## Discussion

With the increasing trend of offering balloon angioplasty for claudication, there is a need for reliable non-invasive arterial assessment. The problem with duplex scanning of the iliac vessels is that it is difficult in obese patients, and bowel gas can preclude good visualization of the vessels[7–10]. Another area in which difficulty in imaging is sometimes found is at the adductor hiatus, although such difficulty may be overcome using a 2·25-MHz phased array probe. For the evaluation of vessels the authors relied mainly on velocity measurements rather than the B-mode image and did not attempt to characterize lesions with respect to degree of calcification or plaque haemorrhage.

For claudicants in whom femorodistal bypass is not an ideal choice – those with mild symptoms, bilateral disease or who are unfit – the dilemma arises as to whether or not angiography should be performed. Angiography is associated with morbidity and mortality[5] and even in the present small series there was one angiogram-related death. An important factor in determining whether or not angioplasty is possible is the state of the origin of the superficial femoral artery; this must be patent to allow a guidewire to be passed into and down the artery. Also, for the purposes of this study, an occlusion $>10$ cm was considered unsuitable for angioplasty, although the maximal length of occlusion that can be successfully treated by endoluminal therapy is variable and controversial[17–22]. Both the superficial femoral artery origin and the length of occlusions are accurately assessed by Duplex scanning.

The PGR results confirmed previous findings that angiography underestimates the number of patent distal calf vessels[11,23]. However, other than providing a more detailed assessment of the distal run-off PGR did not directly help in determining the suitability of a lesion for angioplasty. It does, however, raise the question of the accuracy of studies on angioplasty where the effect of distal run-off, judged by angiography, has been correlated with outcome[18–23].

The costing of the examinations includes personnel and depreciation and is similar to that quoted by other investigators[24]. If a programme of duplex assessment of claudicants with clinically suspected infrainguinal disease had been used on the present cohort of patients, £8062 might have been saved. Duplex scanning could be performed as a simple screening test at the time of the initial clinical visit, thereby allowing more appropriate use of angiography facilities. The most important feature to elicit from the examination would be the status of the origin of the superficial femoral artery[25], but in this group of patients, whose lesions do not threaten life or limb, the occasional failure to identify a patient suitable for angioplasty should not be considered a serious indictment of the test.

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# Selection for screening for familial aortic aneurysms

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*The reported familial clustering of abdominal aortic aneurysm (AAA) indicates the possible rewards of family-based screening programmes with respect both to the number of asymptomatic aneurysms detected and to identifying associated genes. Ultrasonographic screening of 28 families (25 brothers and 28 sisters) was carried out together with collecting a history and a blood sample for analysis of the cholesterol level and genetic markers. Among the screened siblings six (11 per cent), all >60 years old, had an AAA ⩾3·0 cm in diameter. A further 11 siblings (21 per cent), six of whom were <60 years old, had a wide (2·5–2·9 cm) aorta. The presence of an aneurysmal or wide aorta was significantly associated with smoking (P = 0·027), male sex (P = 0·008) and a proband age of <60 years (P = 0·031). Polymorphic genetic markers for type III collagen and haptoglobin were not informative in these families. These results indicate that the efficiency of screening siblings of patients with AAA could be improved by limiting it to brothers with a smoking history and/or siblings of younger patients. The familial component appears to be greatest in these younger patients.*

In all medical specialties there is an increasing emphasis on screening and preventative healthcare: prevention is better than cure. Screening for abdominal aortic aneurysm (AAA) could both prevent the catastrophic event of rupture and provide the scientific information necessary to design a cure. AAA is common in the elderly population and the incidence appears to be increasing[1]. Population screening programmes[2,3] have indicated an incidence of 1·5–4 per cent. Screening of patients with peripheral arterial disease or of siblings of patients with AAA increases the yield to >10 and >25 per cent respectively[4–6]. This last mode of screening, through family members, is perhaps the most interesting; the relatives of a patient are usually anxious to cooperate and, if AAA has a genetic basis, such screening provides the opportunity to investigate the gene(s) involved.

The increasing evidence that AAA has a genetic basis has been reviewed recently[7]. In a single family AAA has been associated with a mutation in type III collagen which has not been demonstrated in other patients with AAA[8]. The mutations associated with other collagen diseases, e.g. osteogenesis imperfecta and Ehlers–Danlos syndrome, are heterogeneous and it has been suggested that a similar situation may exist for aneurysm[7].

The elective repair of an AAA is a safe, durable procedure, yet each year the number of deaths from ruptured aneurysm increases[1]. Do we need to look for a cure? The gene for Marfan's syndrome has recently been identified and there is optimism that this will provide the basis for preventative medicine[9]. Similarly, understanding the cause of AAA could stimulate more preventative care.

## Patients and methods

Consecutive patients attending this hospital for AAA repair were interviewed about their families and family histories, and a blood sample (10 ml anticoagulated with ethylenediamine tetra-acetic acid) obtained. Attention was focused on those with one or more living siblings in England and Wales. A total of 57 siblings of 28 patients (25 men, three women) were contacted. Four siblings (7 per cent) declined to participate in the screening programme.

The families were visited in their homes and a brief history taken concerning cardiovascular disease, hypertension and smoking habit. The maximum external anteroposterior infrarenal aortic diameter was measured using an Aloka 500 portable ultrasonography scanner (Keymed, Southend-on-Sea, UK) equipped with a 3·5-MHz probe. A blood sample was taken for the measurement of the cholesterol level, determination of haptoglobin phenotype, and for isolation of DNA from the white blood cells. Aortic diameters were placed into three categories: <2·5 cm (normal), 2·5–2·9 cm (wide), and ⩾3·0 cm (aneurysmal). General practitioners were advised of any finding of an aneurysmal aorta in their patient.

The polymerase chain reaction was used to amplify a portion of the type III collagen gene from the DNA isolated from the peripheral leucocytes[10,11]. The amplified fragments were digested with restriction enzymes NciI or AluI to look for the Gly–Arg-619 mutation and the common Ala–Thr-581 polymorphism[10,11].

Results were analysed using the $\chi^2$ test with Yates' correction.

## Results

A total of 53 siblings, 25 brothers and 28 sisters, were screened for AAA. Their median age was 65 (range 43–83) years. Among these siblings six aneurysmal aortas (11 per cent) and 11 wide aortas (21 per cent) were found. The aortic diameters are shown in *Figure 1*. The mean(s.d.) age of siblings with wide aortas was 63·5(9·2) years and that of those with aneurysmal aortas 70·7(11·6) years ($P$ = 0·095). The two largest aneurysms have been repaired electively.

Of the 53 siblings, 34 (64 per cent) had a smoking history of >10 pack-years (i.e. at least 10 years of smoking 20 or more cigarettes per day), comprising 21 of 25 brothers (84 per cent) and 13 of 28 sisters (46 per cent). Among smokers there were four aneurysmal aortas and 11 wide aortas, compared with two aneurysmal aortas among non-smokers ($P$ = 0·027). Of the 25 brothers, five had aneurysmal and eight wide aortas, compared with one aneurysmal and three wide aortas in the 28 sisters ($P$ = 0·008). Eight of the probands (Charing Cross patients) had presented for elective aneurysm repair before the age of 60 years; in these families nine of 16 siblings had a wide or aneurysmal aorta compared with only eight of 37 siblings in the other families ($P$ = 0·031).

The mean(s.d.) cholesterol level in the probands was 6·6(1·3) mmol l$^{-1}$, in the siblings with wide or aneurysmal aortas 6·5(1·1) mmol l$^{-1}$, and in the unaffected siblings 6·5(1·3) mmol l$^{-1}$. The presence of a wide or dilated aorta was not associated with a history of hypertension. The haptoglobin phenotypes of 28 probands and their siblings were determined;

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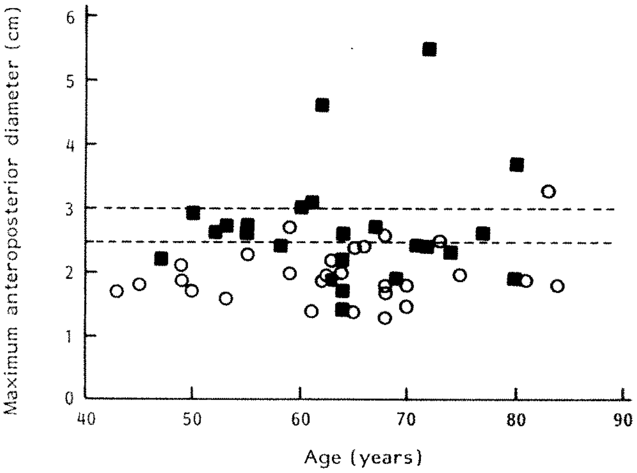

**Figure 1** *Age and anteroposterior aortic diameter for 53 screened siblings.* ■, *Men;* ○, *women*

the normal frequency of the $\alpha_1$ subunit (0·36) among the probands and their siblings indicated that this was not a useful marker. The Gly–Arg-619 type III collagen mutation was not observed in any of the probands. The frequency of Thr at position 581 in type III collagen is 0·32 in the normal population[11]. The frequency of Thr-581 among both the probands and their relatives was lower than this, 0·18, and indicated that this polymorphism was not useful as a marker of familial aneurysm.

## Discussion

The yield of AAA from our family screening programme was much lower than that from either the Oxford or Malmö screening programmes but was similar to the yield in a recent family screening study in North America[5,6,12]. Some of these differences might be attributed to the varying ages of the siblings screened. AAA is a disease of later life. The mean age of the siblings with aneurysms detected by screening was 70·7 years, whereas half of the siblings screened in this study were <65 years old. A group of siblings with wide aortas, >1 s.d. above a mean population aortic diameter, was also defined[2,13]. Interestingly, in this group of 11 siblings with wide aortas, six were <60 years old. It has recently been suggested[14] that the mean growth rate of these wide aortas is 0·11 cm per year, so many of these siblings could have aneurysmal aortas in 5 years. If aneurysmal growth rates are dependent on control of hypertension or continued smoking the identification of wide aortas may be useful in preventative medicine.

The association between smoking and AAA has been convincingly demonstrated in both the Framingham[15] and Whitehall[16] studies. Such epidemiological evidence indicates that smoking is a more specific risk factor for AAA than for coronary heart disease. The present study again indicates that smoking is associated with a higher incidence of AAA. In a small study such as this it is not possible to assess whether male sex is a risk factor independent of smoking. Although more aneurysmal and wide aortas were found among brothers, a smoking history was twice as common among the brothers compared with sisters. With limited resources family aneurysm screening programmes could be restricted to those siblings with a long smoking history.

Perhaps the most effective way to investigate genes involved in aneurysm formation is to establish family pedigrees or collect pairs of affected siblings (who have one-quarter of their genes in common). The familial tendency for dilated aortas was most evident when the proband was <60 years old. For those wishing to pursue 'aneurysm genes' the families of younger patients may be more informative and more of the siblings may still be alive. Polymorphic genetic markers provide most information when a rare variant increases in frequency in the diseased population. Neither the haptoglobin nor the collagen markers used here was informative in this respect and we are now concentrating on alternative approaches to identify aneurysm genes.

Limited budgets are likely to preclude routine screening for AAA in the elderly population. Family screening programmes provide a high yield of wide and aneurysmal aortas. If the risk of developing an AAA depends on age, sex, smoking and aneurysm genes, selected population screening could become a part of future clinical practice.

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# Storage of human pancreatic digest in University of Wisconsin solution significantly improves subsequent islet purification

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*Density-gradient purification of human pancreatic islets from the collagenase-digested pancreas relies on the exocrine tissue being denser than the islets. Cold storage of the pancreas before and after digestion causes cell swelling, which can decrease the density of pancreatic exocrine tissue and adversely affect subsequent purification. Using 14 human pancreata (seven perfused* in situ *with hyperosmolar citrate (HOC) and seven with University of Wisconsin solution (UW)), it is shown that storage of the pancreatic digest in UW significantly increases the density of pancreatic exocrine tissue compared with storage in minimal essential medium (MEM)* ($P = 0.009$)*. This results in an improvement in islet purity* ($P = 0.036$) *for HOC- but not UW-perfused pancreata. Storage in UW for 1 h not only prevented the deterioration that occurred in MEM, but resulted in an improvement in islet purity for five of the seven HOC-perfused pancreata. Most pancreata in the UK are perfused with HOC, but storage of the digest in UW results in significantly better islet purity and, when islets cannot be purified immediately, a period of storage will often improve separation and allow islets to be purified.*

The first report of the isolation of human islets[1] was published in 1971; the islets were handpicked from collagenase-digested pancreas. One year later, the use of density centrifugation for purification was described[2]. This method of separating islets from pancreatic digest depends on the difference in density between the exocrine particles and the less dense islets. Over the intervening 20 years, this has remained the only effective means of separation. The limitations of this technique remain one of the major obstacles to successful islet transplantation, restricting both islet yield and purity.

Damage to the exocrine (non-islet) tissue during the process of digestion[3] results in the release of proteolytic enzymes, a process known to alter tissue density and impair subsequent density separation. When this is coupled to the cell swelling[4] that occurs with cold storage of tissue[5], the resulting changes in tissue density make centrifugation an uncertain and variable process[6].

Digestion of each pancreas can produce as much as 60 ml of digest and even with large-scale separation gradients using the COBE 2991 cell separator (COBE Laboratories, Gloucester, UK)[7] only 15–20 ml can be efficiently purified at any one time. The storage of digest for up to 1 h is therefore unavoidable. This may significantly impair purification by causing the density of the exocrine tissue to decrease.

Until recently pancreatic digest in this unit was stored in minimal essential medium with Hanks' salts (MEM); other groups use media such as Hanks' balanced salt solution[8–10], which has a similar electrolyte formulation but lacks the amino acids and vitamins. Recent work in the dog[11] has suggested that storage in University of Wisconsin solution (UW) could improve islet purification. UW has also been shown to improve the yield of islets from human pancreas where a period of cold storage before digestion is unavoidable[12], and to improve the results of whole organ transplantation after cold storage[13,14] by reducing cell swelling and expansion of intracellular fluid[15] and improving the viability of islets[12,16]. This study examined the effect of UW on storage of pancreatic digest during purification of islets using 14 consecutive human pancreata.

## Materials and methods

Fourteen consecutive human pancreata retrieved with appropriate consent from brain-dead heart-beating organ donors were studied. After randomization using sealed envelopes, seven pancreata (nos 1, 3, 5, 8, 9, 10 and 12) were perfused *in situ* with hyperosmolar citrate (HOC) and the other seven with UW. The cold ischaemic time was <3 h in each case.

The pancreas was digested at 38°C using a standardized technique modified slightly from that described by Ricordi *et al.*[17]. Intraductal distension[8] was performed throughout with the same batch of collagenase (Serva; Feinbiochemica, Heidelberg, Germany). The resulting digest was collected into MEM (Northumbria Biologicals, Cramlington, Northumberland, UK) containing 10 per cent newborn calf serum. Then 1 ml digest was washed twice in MEM and another 1 ml washed twice in UW (Belzer UW–CSS; Du Pont, Wilmington, Delaware, USA). From each digest, 100 μl of tissue was immediately suspended in 1 ml 1·106 g/cm$^{3}$ high-density 500 mOsmol/kg bovine serum albumin (BSA; Advanced Protein Products, Brockmoor, Brierley Hill, UK). This was overlaid with BSA using a continuous-gradient maker (Hoefer SG100; Hoefer, Newcastle-under-Lyme, UK). By placing 5 ml low-density (1·075 g/cm$^{3}$) BSA in one chamber and 5 ml high-density (1·106 g/cm$^{3}$) BSA in the other, 11-ml BSA gradients were produced in which the density increased linearly from 1·075 to 1·106 g/cm$^{3}$, with constant osmolality. Two such gradients were produced synchronously for both the MEM- and UW-washed digests. They were centrifuged at 800*g* (22°C) for 5 min. The distribution of tissue within the paired gradients was compared visually and in each case appeared identical.

Each gradient was divided into 11 × 1-ml aliquots. The 1-ml fractions were washed twice in MEM and one gradient from the MEM-washed pair and one from the UW stained with dithizone, a zinc-binding dye that stains islets red[18]. Each fraction was then examined under the microscope, and the amount of exocrine tissue and islets in each scored to give a visual estimate of purity. The fractions from the other gradient were resuspended in 2 ml MEM and sonicated before assay of insulin and amylase content.

The remaining digest was resuspended in the same medium as used for the original washing and stored for 1 h at 4°C before two further pairs of gradients were run to examine any change in tissue density that had occurred.

The percentage of insulin and amylase in each of the 1-ml fractions

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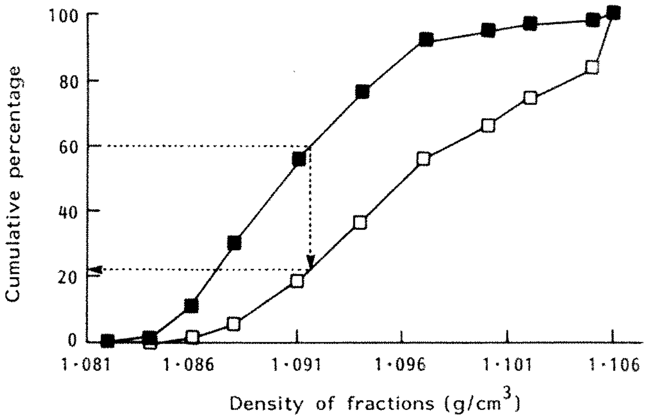

**Figure 1** *Plot of the cumulative distribution of amylase (□) and insulin (■) in tissue down a gradient, to determine the percentage exocrine contamination for any islet yield. The percentage exocrine contamination of a 60 per cent yield of islets is illustrated*

was determined. The density distributions of insulin and amylase were plotted to determine changes in the peak density. The cumulative percentage of insulin was plotted against that of amylase to determine the percentage of the total exocrine tissue contaminating any percentage of islets (*Figure 1*). As a measure of purity, the exocrine contamination of a 60 per cent yield of islets was used to compare treatments, to eliminate the influence of yield variation on purity.

### *Statistical analysis*

Pearson's product–moment correlation coefficient ($r$) was used to compare the results of visual scoring of tissue distribution on the gradients with that determined by assay.

In both groups (HOC and UW perfused), each pancreas acted as its own control. The changes in peak density of islets and exocrine tissue that occurred with storage in UW were compared with those after storage in MEM using the Wilcoxon matched pairs signed rank test (reported as Wilcoxon statistic ($T$) with $P$ value); the Wilcoxon signed rank-based 95 per cent confidence interval (c.i.) was determined. Differences in the resulting purity were compared using the same test, and differences between UW- and HOC-perfused pancreata examined using the Mann–Whitney $U$ test and reported as mean ranks with $P$ values.

## Results

The result of each visual scoring of tissue distribution was compared with that determined by assay from its matched gradient. The two were significantly correlated for both islets and insulin (mean $r = 0·65$, $P < 0·02$), and exocrine cells and amylase (mean $r = 0·78$, $P < 0·01$). In addition, the percentages of exocrine contamination of a 60 per cent islet yield for both assessment methods were significantly correlated ($r = 0·54$, $P < 0·05$). The assays were used for all subsequent analyses of tissue distribution.

### *Changes in density of islets and exocrine tissue*

*HOC-perfused pancreata.* The 95 per cent c.i. for the change in peak density of both exocrine and islet tissue with storage is shown in *Figure 2*. The peak islet density changed very little with storage in either MEM or UW. However, the density of the exocrine tissue changed dramatically; storage in MEM decreased and storage in UW increased the exocrine density.

*UW-perfused pancreata.* The changes in exocrine tissue density were very similar to those in pancreata perfused with HOC. However, UW storage of pancreata perfused with UW resulted in an increase in the density not only of the exocrine tissue but also of the islets. This was significantly different (mean $r = 9·86$, $P = 0·04$) from the effect of UW storage on islets from HOC-perfused pancreata (*Figure 2*).

*Overall effect on density.* The density of exocrine tissue was found to change immediately after washing the digest in UW, compared with MEM ($T = 0$, $P = 0·042$). Storage in MEM resulted in a significant decrease in the density of exocrine tissue ($T = 21·0$, $P = 0·036$) and when digest stored in MEM was compared with that stored in UW the exocrine tissue stored in the latter was significantly denser ($T = 0$, $P = 0·009$). In contrast, the density of the islets before and after storage in either MEM or UW did not change significantly.

In practice, this means that storing the digest in MEM results in a significant decrease in the density of exocrine tissue but not islets, which minimizes the initial differences. In contrast, storage of digest in UW results in a significant increase in the density of exocrine tissue but not of islets, thereby increasing the difference in density between the two.

### *Effect of storage on purity of islets*

Microscopic examination after staining with dithizone indicated that a period of UW storage appeared to improve purity, with less exocrine contamination. Storage in MEM, in contrast, resulted in an increase in exocrine tissue in the same density fractions as the islets, and a consequent reduction in purity. The effect of storage media on purity was determined using the assay results.

*HOC-perfused pancreata.* The difference in purity after storage in UW and MEM is shown in *Figure 3*. In all but one

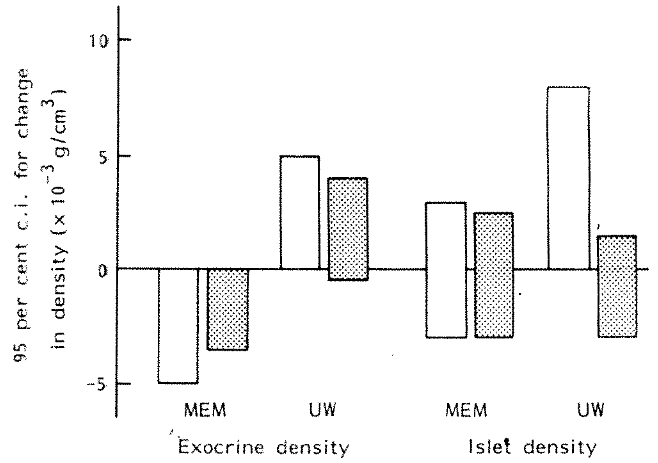

**Figure 2** *Changes in density with storage in the two groups, shown as 95 per cent confidence interval (c.i.). The only significant difference* (P = *0·04, Mann–Whitney* U *test) between HOC (▨) and UW (□) perfusion is in the behaviour of islets stored in UW. HOC, hyperosmolar citrate; MEM, minimal essential medium. UW, University of Wisconsin solution*

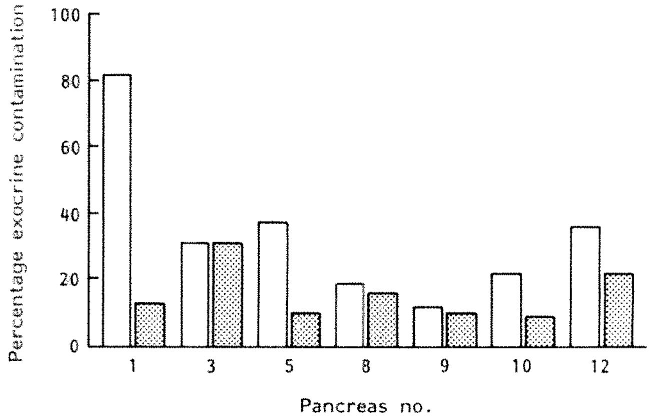

**Figure 3** *Percentages of exocrine contamination for HOC-perfused pancreata after 1-h storage in either MEM (□) or UW (▨). Storage in MEM gave greater contamination* (P = *0·036, Wilcoxon signed rank test). HOC, hyperosmolar citrate; MEM, minimal essential medium; UW, University of Wisconsin solution*

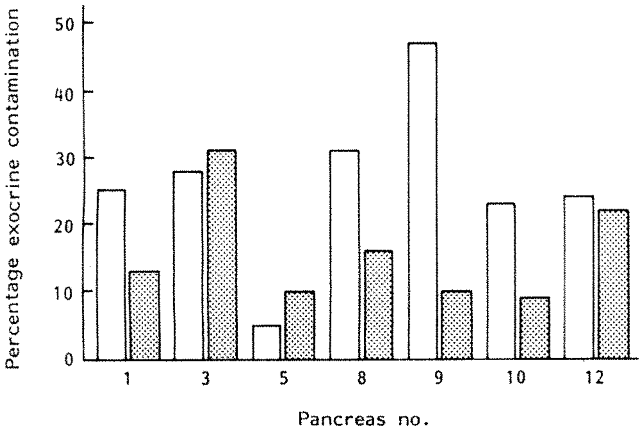

**Figure 4** *Islet purity in HOC-perfused pancreata before (☐) and after (▨) storage for 1 h in UW. Storage resulted in a decrease in exocrine contamination in five of seven pancreata (*P = *0·15, Wilcoxon signed rank test). HOC, hyperosmolar citrate; UW, University of Wisconsin solution*

case, storage in UW was better ($T = 21{\cdot}0$, $P = 0{\cdot}036$). Storage in MEM resulted in a median increase in exocrine contamination of +10 (95 per cent c.i. −5·5 to +36·5) per cent. Storage in UW resulted in an improvement in islet purity in five of the seven pancreata compared with the purity achieved initially (*Figure 4*), with exocrine contamination being reduced by a median of −12 (95 per cent c.i. −25·5 to +3) per cent.

*UW-perfused pancreata.* The fact that storage in UW increased the density of the islets as well as of the exocrine tissue meant that storage in UW was not significantly better than storage in MEM, and storage for 1 h in UW did not result in any improvement in islet purity.

*Comparison of HOC- and UW-perfused pancreata.* No significant differences in purity existed between the two groups or between stored and fresh digests.

## Discussion

The methods used for assessing changes in density and purity rely on assessment of the distribution of tissue on linear continuous-density gradients. The high correlation between the visual assessment of tissue distribution and that determined by subsequent assay shows that the assay results after tissue disruption by sonication accurately represent the distribution of tissue on the gradient.

The visual assessment of exocrine contamination of a 60 per cent islet yield also correlated significantly with that determined by assay. However, there is no doubt that visual assessment of islet numbers becomes less accurate as fractions containing large amounts of exocrine tissue are examined, as does the quantifiation of exocrine tissue itself. The use of assays avoids this subjective error.

The medium in which the digest is stored significantly affects the density of the tissue. The reasons for this change are likely to be due to the lactobionate and raffinose contained in UW, which are thought to prevent cell swelling, and the hydroxyethyl starch, which prevents expansion of the extracellular space[5,15]. The question of whether $Na^+$ or $K^+$ as the major cation affects cell swelling is debatable[15,19]. Because separation of exocrine tissue from islets relies on density centrifugation, such changes are of major importance and affect the degree of exocrine contamination of the purified islets.

For HOC-perfused pancreata (which include the majority of those retrieved for pancreatic islet transplantation in the UK), storage of the digest in UW significantly decreases exocrine contamination compared with storage in MEM, and exposure to UW for a period of 1 h improves the purity of the islets compared with immediate separation.

The significance of the changes in exocrine contamination can be appreciated when it is remembered that 98 per cent of the pancreas is exocrine tissue. This means that if all the islets are isolated (100 per cent yield), together with only 1 per cent of the exocrine tissue, the result will be islets which are only 50 per cent pure. If the proportion of exocrine tissue retained increases by 1 per cent, the purity of the islets falls to 33 per cent.

In practice, the improvement seen using UW was so dramatic that, after storage, digest could be purified from some pancreata from which islets could not initially be separated. The fact that this effect results from an increase in the density of the exocrine tissue suggests that UW may not only prevent but reverse the cell swelling to which the exocrine tissue appears particularly sensitive. This means that a period of storage can actually be beneficial.

In addition to its effect on cell swelling, there is also evidence that UW results in less damage to exocrine tissue during storage, as higher levels of urinary amylase are seen after whole organ transplantation[14]. By preventing exocrine damage in this way, storage of the digest in UW may maintain its density and further aid islet purification.

Although it had been hoped that *in situ* perfusion of the pancreas with UW rather than HOC might further increase this effect, the only significant difference that resulted was an increase in the density of islets after storage in UW. This negated the advantage of UW storage in HOC-perfused pancreata, where increased exocrine density only was observed. Although UW perfusion is useful if prolonged periods of cold ischaemia are envisaged, it does not improve islet purity. One reason for this may be that collagenase digestion appears to be less effective after UW perfusion, resulting in islets remaining attached to fragments of exocrine tissue. This would explain why islets from UW-perfused pancreata appear to behave like exocrine tissue during density-gradient separation.

In conclusion, pancreatic digest should be stored in UW to prevent and reverse exocrine cell swelling, and to enhance islet purity. If islets cannot be purified immediately, a period of storage in UW can result in a dramatic improvement and may allow islets to be separated. Further studies are currently underway to examine which components of the UW are beneficial, to allow their incorporation into the density-gradient media.

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# Randomized trial of loop ileostomy in restorative proctocolectomy

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*A randomized controlled trial was performed to assess the role of loop ileostomy in totally stapled restorative proctocolectomy. Entry criteria included all patients who were not on corticosteroids in whom on-table testing revealed a watertight pouch with intact ileoanal anastomosis. Of 59 patients undergoing restorative proctocolectomy over 36 months, 45 were eligible and were randomized to loop ileostomy* ($n = 23$) *or no ileostomy* ($n = 22$). *The age and diagnosis of the groups were similar. There were no deaths; two ileoanal anastomotic leaks occurred, one in each group. Ileoanal stenosis occurred in five patients with and one without an ileostomy. The incidences of wound and pelvic sepsis, bowel obstruction and pouchitis were similar. Twelve patients (52 per cent) developed ileostomy-related complications. The median total hospital stay was 23 (range 13–75) days with ileostomy and 13 (range 7–119) days without* ($P < 0{\cdot}001$). *This study indicates that there is a low risk of pelvic sepsis which is not increased by avoiding a protective ileostomy. Loop ileostomy was associated with a high incidence of complications.*

Restorative proctocolectomy with construction of an ileal pouch–anal anastomosis has an established role in the surgical management of ulcerative colitis and familial adenomatous polyposis[1–4]. The operation involves excision of the colon and rectum with all diseased mucosa and avoids the need for a permanent intestinal stoma. Pelvic sepsis remains a serious potential complication of the procedure and may subsequently compromise the functional outcome. Numerous technical modifications and increasing experience have resulted in diminished morbidity from sepsis and fistulae, with improved functional results[5,6]. Nevertheless, most authors still advocate the routine use of a temporary defunctioning ileostomy during the period of anal and ileal anastomotic healing to protect patients from the consequences of anastomotic leakage and pelvic sepsis.

However, the ileostomy itself may be an important source of postoperative morbidity. Modifications in stoma technique or avoidance of a temporary ileostomy may improve results[7,8]. Several studies have reported the results of restorative proctocolectomy without a covering ileostomy[9–14]. In most of these series only a small proportion of selected cases did not have a covering stoma; nevertheless the omission of an ileostomy did not appear to increase the risk of anastomotic complications.

This paper reports a randomized controlled clinical trial to assess the risks or possible benefits of performing restorative proctocolectomy with or without a protective ileostomy.

## Patients and methods

### *Study design*

Of 59 patients admitted for elective restorative proctocolectomy during the 3 years between September 1988 and August 1991, 45 were eligible for the trial. All patients underwent a standardized totally stapled abdominal restorative proctocolectomy as previously described[15] and performed by, or under the direct supervision of, one surgeon (M.R.B.K.). Entry criteria stipulated that the surgeon had to be satisfied that conduct of the procedure was uncomplicated and that all anastomoses were intact on intraoperative testing. After completion of the ileoanal anastomosis, the 45 eligible patients were randomized as described below, 23 to receive a loop ileostomy and 22 no ileostomy.

Fourteen patients were excluded for the following reasons: coexisting administration of systemic steroids ($n = 2$); megarectum, which made it impossible to use the double stapling technique ($n = 5$); an S pouch was constructed because of inadequate mesenteric length ($n = 2$); anal canal fibrosis made a stapled ileoanal anastomosis impossible ($n = 1$); operative damage to the anal canal occurred ($n = 1$); and failed stapling was detected by intraoperative testing ($n = 3$).

Ethical approval for the protocol was obtained from the Birmingham Hospitals Research Ethical Committee. Patients who participated in the study gave informed consent before surgery.

The primary endpoint of the trial was the development of pelvic sepsis or leakage from the pouch or ileoanal anastomosis. Additional factors contributing to postoperative morbidity that were analysed included ileoanal stenosis, bowel obstruction, ileostomy-related complications and functional outcome. Factors assessed relating to the cost of treatment were the duration of theatre utilization and hospital stay.

### *Operative procedure*

*Restorative proctocolectomy.* The technique was identical throughout the study period with the exception of the use or otherwise of an ileostomy[15]. After colectomy or mobilization of an ileostomy, the distal ileum was transected with a linear stapling device. After mobilization, the linear stapler was applied across the upper anal canal at the proposed anastomosis site, the anal canal was transected and the rectum removed. A double-limb 20 × 20 cm J pouch was constructed by multiple application of a linear stapler–cutter. Before pouch–anal anastomosis, saline was introduced under moderate pressure into the pouch to identify leaks in the staple lines.

End-to-side ileoanal anastomosis was performed using the Premium CEEA28 circular stapler (Auto Suture, Ascot, UK), placed carefully through the centre of the anal staple line. The integrity of the anastomosis was assessed by digital examination through the anus, by air insufflation of the pouch after filling the pelvis with saline, and by the recovery of two complete 'doughnut' rings from the circular stapler.

In patients randomized to ileostomy a stomal aperture was made at a predetermined site through the rectus abdominis in the right lower quadrant. A loop of ileum was identified that would reach the abdominal wall without creating tension on the pouch (average 50 cm proximal to the pouch). A 30-Fr latex catheter was inserted through the anal anastomosis into the pouch and sutured to the perianal skin. Two or three closed suction drains were placed in the pelvis. After closure of the abdominal wound, the loop ileostomy was constructed in a standard manner[16] by eversion of the proximal ileum and mucocutaneous suture without a supporting rod or rotation of the limbs[17].

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*Ileostomy closure.* Assessment before closure included clinical and endoscopic examination with manometry; pouch contrast radiography was not routinely performed. Ileostomy closure was performed in all 22 patients as a local procedure through a circumstomal incision. The operation was carried out by a consultant surgeon ($n = 14$) or one of two senior registrars. In 21 patients the stoma was completely mobilized and the enterotomy closed transversely in one or two layers after freshening the edges. In one patient the stoma site was resected and end-to-end anastomosis performed. After closure of the rectus sheath the skin defect was left open.

### *Follow-up*

All patients were seen at 1, 3 and 6 months and thereafter twice yearly for interview, clinical examination and pouch endoscopy. Complications and functional results were recorded. The median follow-up after restorative proctocolectomy was 20 (range 4–41) months.

### *Statistical analysis*

Randomization and analysis were performed by one of two research associates not directly involved in the operations. The randomization was in equal proportions in blocks of six or eight from random number tables, but without stratification for age, sex or diagnosis. It was estimated that 100–120 patients would be required to provide a 90 per cent power in demonstrating an increase in septic complications from 10 to 20 per cent by omission of a protective ileostomy ($\alpha = 0\cdot05$). An interim assessment was planned at 3 years (60–75 patients expected to be enrolled). Statistical analyses included the Wilcoxon rank sum test for comparing continuous variables and $\chi^2$ (with Yates' correction) and Fisher exact tests for proportions. Statistical significance was taken as $P < 0\cdot05$. The data are presented as median (range) unless otherwise specified.

## Results

The ages of patients in both groups were similar but there was a preponderance of female patients in the group without ileostomy ($P = 0\cdot04$) (*Table 1*). Half of the patients in both groups had undergone colectomy before the pouch procedure. The majority of the operations were performed for ulcerative colitis, but the series included patients with familial adenomatous polyposis, slow-transit constipation and multiple dysplastic colorectal polyps (*Table 1*). Two patients thought to have ulcerative colitis before the operation were diagnosed as having Crohn's disease after synchronous colectomy and pouch formation.

**Table 1** *Comparison of patients in the study groups*

| | Loop ileostomy ($n = 23$) | No ileostomy ($n = 22$) |
|---|---|---|
| Median (range) age (years) | 33 (15–80) | 34 (15–50) |
| Sex ratio (M:F) | 13:10 | 5:17† |
| Previous colectomy* | 12 (52) | 11 (50) |
| Previous ileostomy | 7 | 10 |
| Ileorectal anastomosis | 5 | 1 |
| Diagnosis | | |
| Ulcerative colitis | 15 | 16 |
| Familial adenomatous polyposis | 3 | 6 |
| Slow-transit constipation | 3 | 0 |
| Multiple dysplastic polyps | 2 | 0 |

*Values in parentheses are percentages. †$P = 0\cdot04$ ($\chi^2$ test)

**Table 2** *Postoperative complications*

| | Loop ileostomy ($n = 23$) | No ileostomy ($n = 22$) |
|---|---|---|
| Pouch related | | |
| Ileoanal leak (and pelvic sepsis) | 1 | 1 |
| Ileoanal stenosis* | 5 (22) | 1 (5) |
| Major wound sepsis† | 2 (surgery) | 1 (conservative) |
| Pelvic haemorrhage† | 0 | 1 (ileostomy) |
| Ischaemia† | 0 | 1 (excision) |
| Bowel obstruction* | 5 (22) | 2 (9) |
| Conservative:surgery | 2:3 | 2:0 |
| Pouchitis | 2 | 5 |

*Values in parentheses are percentages; †treatment of complications is summarized in parentheses

### *Complications*

There were no postoperative deaths. Although pouch-related complications tended to be more common in patients with a covering ileostomy, this difference was not statistically significant (*Table 2*). Only two leaks occurred from the ileoanal anastomosis, one in each group. A partial dehiscence at the ileoanal anastomosis was detected 14 days after restorative proctocolectomy in a patient with a covering ileostomy. A contained pelvic abscess developed that resolved under conservative management. The ileostomy was closed 4 months later, but the patient suffers from frequency, urgency and incontinence. The only patient in the unprotected group in whom a leak occurred developed pelvic sepsis from a dehiscence of the ileoanal anastomosis 7 days after restorative proctocolectomy. The anastomosis was disconnected and the pouch brought out as an end ileostomy. After 6 months the pouch was reanastomosed to the anal canal, but the patient developed a complex pouch–vesical–abdominal wall fistula. This was managed surgically by resection with a covering loop ileostomy. The ileostomy has now been successfully closed with a good functional result.

One patient without a covering ileostomy required early relaparotomy and pelvic packing for unidentifiable pelvic haemorrhage; a protective ileostomy was raised in this case because of fears that the ileoanal anastomosis might have been disturbed. The ileostomy was later successfully closed.

Bowel obstruction occurred more frequently in the patients with an ileostomy than in those without (five *versus* two cases). In patients with an ileostomy, two episodes of bowel obstruction were managed conservatively, but three required surgical intervention. In all three cases the mechanical obstruction was related to the ileostomy site. Bowel herniation lateral to the limbs of the loop ileostomy occurred in one patient, which required taking down of the ileostomy to release the obstructed bowel whereafter the stoma was re-established; in the other two cases, adhesive bands in the vicinity of the stomal closure site caused mechanical obstruction. In one case 30 cm of infarcted bowel was resected in a young boy with familial adenomatous polyposis. The two cases of bowel obstruction in the group with no ileostomy were both managed conservatively.

One or more ileostomy-related complications occurred in twelve of the 23 patients in the ileostomy group. Five patients with severe ileostomy flux required hospital admission for rehydration and electrolyte replacement. In three cases early ileostomy closure was indicated because of repeated dehydration. Stomal retraction occurred in three patients and caused troublesome skin and appliance problems; furthermore, the stomas failed to divert the faecal stream adequately. An ileocutaneous fistula developed from the ileostomy closure site in one patient. This was successfully managed conservatively. Two stomal hernias later required repair.

The operating times and hospital stay for the initial restorative proctocolectomy were similar for both groups (*Table 3*). Although the ileostomy closure entailed an additional operation (median 45 (range 30–85) min) and readmission (hospital stay 8 (4–35) days), an excess of complications further contributed to significantly longer theatre utilization and total hospital stay in the ileostomy group ($P < 0\cdot001$) (*Figure 1*). These factors were major contributors to overall treatment costs, which were greater for the patients in the ileostomy group than for those without an ileostomy.

The median follow-up between the two groups was comparable, taking into account the 2–5 months between restorative proctocolectomy and ileostomy closure in the ileostomy group. Functional results were similar in both groups (*Table 4*). In one patient the ileostomy has not yet been closed

**Table 3** *Theatre utilization and hospital stay*

| | Loop ileostomy ($n$ = 23) | No ileostomy ($n$ = 22) |
|---|---|---|
| Reoperation* | 9 (39) | 3 (14) |
| Relaparotomy* | 4 (17) | 3 (14) |
| Median (range) operating time (min) | | |
| Pouch | 160 (100–270) | 150 (110–210)† |
| Total | 220 (130–380) | 158 (110–620)‡ |
| Median (range) hospital stay (days) | | |
| Pouch | 11·5 (7–33) | 12 (7–44)† |
| Total | 23 (13–75) | 13 (7–119)‡ |

*Values in parentheses are percentages; data exclude ileostomy closure. †$P$ not significant; ‡$P < 0{\cdot}001$ (Wilcoxon rank sum test)

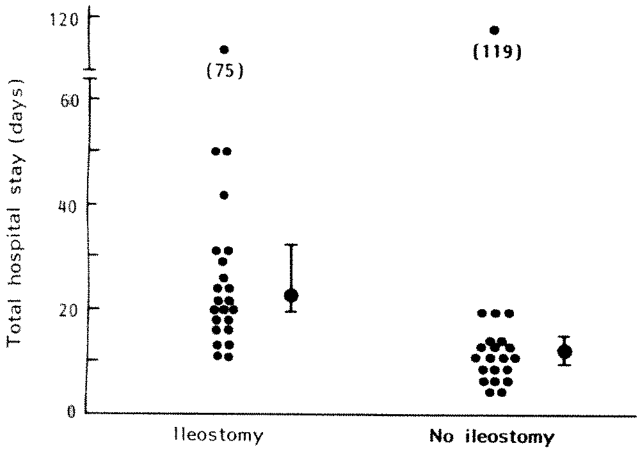

**Figure 1** *Total hospital stay. Bars are median (95 per cent confidence interval). Hospitalization was significantly longer in the group with an ileostomy (P < 0·001, Wilcoxon rank sum test)*

**Table 4** *Pouch function*

| | Loop ileostomy ($n$ = 23; one ileostomy not yet closed) | No ileostomy ($n$ = 22; one pouch excised) |
|---|---|---|
| Median time to ileostomy closure (months) | 3 (2–5) | — |
| Median follow-up (months) | 17 (4–39) | 24 (6–41) |
| Median stool frequency (D:N) | 5:1 | 5:1 |
| Nocturnal soiling | 5 | 4 |
| Incontinence | 2 | 0 |

Values in parentheses are ranges. D:N, daytime:night-time

because of patient preference and one pouch was excised in the early postoperative period.

### *Exclusions*

Preoperative evaluation excluded seven patients from the trial as already indicated. Neither patient on steroids received a covering ileostomy initially, but both developed life-threatening complications and required temporary ileostomies. Pelvic sepsis with septicaemic shock occurred in one, but no evidence of an anastomotic leak could be demonstrated at relaparotomy. The other patient developed a dehiscence at the ileoanal anastomosis resulting in a recurrent fistula. This patient was later found to have Crohn's disease. In one of the five patients with megarectum a protective ileostomy was not raised; the patient subsequently developed a leak from the ileoanal anastomosis requiring relaparotomy and a diverting ileostomy. In the seven patients excluded because of intraoperative technical difficulties, temporary loop ileostomies were raised and later successfully closed.

## Discussion

Loop ileostomy is the most frequent method of temporary diversion employed after restorative proctocolectomy. Although Lewis and Bartolo reported that loop ileostomy closure can be achieved with a low morbidity rate[18], complications from the ileostomy and its closure have been reported in 30–59 per cent of patients[7,8,10,19]. Although stomal complications are seldom life-threatening, they contribute significantly to the morbidity of the procedure. The benefits of defunctioning the pouch should, therefore, be weighed against the complications produced by the covering stoma. Intestinal obstruction occurs commonly after restorative proctocolectomy, and approximately half of these cases require surgical intervention[20]. The construction of a loop ileostomy and its subsequent closure may contribute to the development of small bowel obstruction.

Several workers have contemplated performing restorative proctocolectomy without an ileostomy. Initial reports with small numbers indicated that the stoma could be safely omitted in carefully selected patients[21,22], but others have sounded cautionary notes[23]. In a study by Everett and Pollard[9], 29 of 64 selected patients who underwent hand-sewn restorative proctocolectomy with a W reservoir without an ileostomy benefited from a lower incidence of complications and total hospital stay. In two Finnish series, a high proportion of restorative proctocolectomies with hand-sewn ileoanal anastomoses were performed without a covering ileostomy[10,11]. The results of avoiding a covering loop ileostomy were generally satisfactory, but one of 25 and three of 50 patients required later diversion for postoperative sepsis. In the large Mayo Clinic series, only 37 of 1027 patients underwent ileal pouch–anal anastomosis without diverting ileostomy; anastomotic leakage occurred in two of these patients[12]. Sugerman *et al.* reported on 19 patients with an unprotected stapled ileoanal anastomosis; although the majority of these were either on steroids or undergoing semiurgent procedures, only three developed pelvic sepsis[13].

This study has demonstrated a low risk of anastomotic and septic complications; it appears that this risk was not increased by omitting an ileostomy. More importantly, a high number of ileostomy-related complications were encountered. Furthermore, avoiding a covering ileostomy has resulted in significant financial savings in terms of theatre utilization and hospital stay, and may permit earlier return of the patient to their normal role in society.

In this interim analysis of a randomized clinical trial, recruitment was lower than expected in 3 years. The study has the advantage that a single experienced surgeon used a standardized operation technique. Although baseline characteristics were reasonably matched, the excess of female patients in the unprotected group may be a cause for bias. It should be emphasized that the design of the trial should minimize the effect of body build or previous colectomy, as final eligibility was determined only after satisfactory completion and testing of the anastomosis.

It has been decided to discontinue this trial for three main reasons. First, pouch-related complications were lower than expected and larger numbers of patients than predicted would need to be studied to retain the power of the study. Second, septic complications did not appear to be increased by avoiding an ileostomy, but a cautionary note is in order as the small number of patients studied increases the risk of a Type II error ($\beta = 0{\cdot}4$). Finally, the high rate of ileostomy-related complications meant that there was no justification for continuing a policy in which half of the patients developed ileostomy-related complications that contributed to morbidity and treatment costs.

We do not advocate a single-stage procedure without a covering stoma for all patients. This study provides evidence that restorative proctocolectomy without temporary defunctioning may be a safe alternative. Our criteria for omission of an ileostomy are that the patient should be in good general health without sepsis, not receiving systemic steroids and have a normal-calibre rectum. The surgeon should be suitably experienced and satisfied that all staple lines are intact and without tension at the end of the procedure. We accept that there is a small risk involved in avoiding a defunctioning stoma but the frequency and consequences of an unprotected leak should be offset against the high complication rate of the loop ileostomy.

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# Screening patients with claudication from femoropopliteal disease before angioplasty using Doppler colour flow imaging

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*Time, expense, risk and discomfort are incurred by arteriography in patients with intermittent claudication who might be candidates for percutaneous transluminal angioplasty (PTA). A valid screening technique could reduce the need for arteriography in patients found to have lesions not amenable to PTA. Agreement between Doppler colour flow imaging (DCFI) and angiography for detecting haemodynamically significant lesions is high, but DCFI may not identify lesions suitable for angioplasty. A total of 36 limbs in 30 patients were studied using DCFI before angiography. Agreement between the two methods was excellent ($\kappa = 0{\cdot}91$), and the predictive accuracy of DCFI for lesions amenable to PTA was good ($\kappa = 0{\cdot}78$, sensitivity 94 per cent, specificity 85 per cent, positive predictive value 83 per cent, negative predictive value 94 per cent, overall accuracy 89 per cent). DCFI is a useful screening process that may prevent unnecessary angiography, with consequent financial savings and clinical benefit.*

Since its inception nearly 20 years ago[1], Doppler colour flow imaging (DCFI) has been used diagnostically in a wide variety of vascular problems[2,3]. In lower limb arteries it can distinguish haemodynamically significant from non-significant stenosis, and stenosis from occlusion[4–8]. It may therefore be a reliable screening technique before percutaneous transluminal angioplasty (PTA). Accuracy in diagnosing atherosclerotic lesions does not necessarily equate to predicting suitability for angioplasty as judged by arteriography. A study was therefore carried out to assess the value of screening patients with claudication by DCFI.

The use of angioplasty in the treatment of claudication is usually restricted to stenoses or short occlusions. In 'limb salvage' situations long occlusions are commonly treated and it is accepted that the long-term patency rate is lower[9]. A screening technique for patients with claudication needs to distinguish short from long lesions and significant from non-significant stenoses. The true predictive value of DCFI in this context would allow estimation of the savings.

## Patients and methods

Patients with intermittent claudication from femoropopliteal disease were studied. The diagnosis was made if the patient gave a clear history of calf claudication, had an easily palpable femoral pulse and a weak or absent popliteal pulse. If symptoms were significantly disabling the option of angioplasty was discussed, and consent was obtained for angiography proceeding to PTA if a suitable lesion was found. The superficial femoral artery was assessed by uniplanar views only. The definition of a 'suitable' lesion was the angiographic finding of a stenosis narrowing the luminal diameter by $>50$ per cent or a discrete occlusion $\leqslant 10$ cm in length (the length of the occlusion being the same as the length needing dilatation and the remainder of the arterial tree having no haemodynamically significant disease). On the day before angiography all patients underwent DCFI of the femoropopliteal segment using an Ultramark 9 (Advanced Technology Laboratories, Bothell, Washington, USA) ultrasonography system with a 5-MHz transducer. Significant stenosis[4] was recorded where velocity increased by $>100$ per cent. This was taken to mean the lesion could be appropriately treated by PTA. A lesion considered unlikely to be treatable by angioplasty (a negative result) was a length of stenosis or occlusion $>10$ cm. Length was determined by skin-marking the sites at the start and end of the occlusion and measuring between them. The ultrasonographic findings were not available to the radiologist until a decision had been made on whether or not to perform angioplasty.

### *Statistical analysis*

The kappa statistic ($\kappa$), which takes into account agreement by chance, was used to measure the agreement between the two methods of diagnosis; a $\kappa$ value of 1·0 represents perfect agreement, and one of 0 represents agreement no greater than that predicted by chance alone[10].

## Results

A total of 36 limbs in 30 patients (median age 65 (range 45–85) years) were studied. The femoropopliteal segment was visualized in all patients. Predominantly unilateral symptoms were present in 24 patients and the worse leg was scanned. In six patients claudication was bilateral and equal, and both legs were scanned.

### *Agreement over detection of lesions*

The findings detected by DCFI and angiography are shown in *Table 1*. The data show the concordance between the methods.

In 26 limbs an occlusion was demonstrated by both methods. In three limbs the length of occlusion could not be measured easily by DCFI. In another three limbs (two patients) the length of occlusion could not be determined because it extended into the tibioperoneal trunk. In one patient angiography did not

**Table 1** *Concordance between lesions detected by Doppler colour flow imaging and by angiography*

| | Angiography | | | |
|---|---|---|---|---|
| | Occlusion | Stenosis | Normal* | Total |
| Doppler colour flow imaging | | | | |
| Occlusion | 26 | 1 | 0 | 27 |
| Stenosis | 0 | 14 | 1 | 15 |
| Normal* | 0 | 0 | 1 | 1 |
| Total | 26 | 15 | 2 | 43 |

*Defined as $\leqslant 50$ per cent stenosis. $\kappa = 0{\cdot}91$

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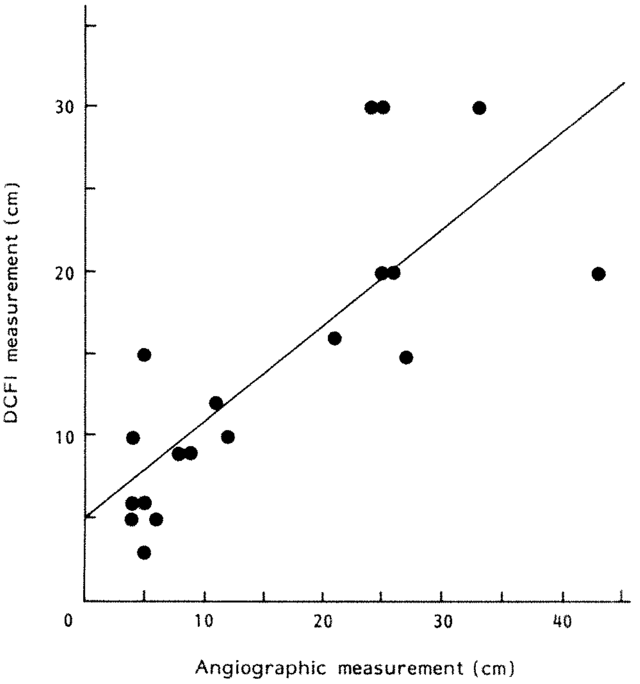

**Figure 1** *Correlation between length of femoral artery occlusion measured by Doppler colour flow imaging (DCFI) and angiography.* $r = 0{\cdot}79$

**Table 2** *Concordance between Doppler colour flow imaging prediction of suitability for percutaneous transluminal angioplasty and that found after arteriography*

| | Angiography | | |
|---|---|---|---|
| | Positive | Negative | Total |
| Doppler colour flow imaging | | | |
| Positive | 15 | 3 | 18 |
| Negative | 1 | 17 | 18 |
| Total | 16 | 20 | 36 |

Positive, prediction that percutaneous transluminal angioplasty (PTA) is possible; negative, prediction that PTA is not possible. $\kappa = 0{\cdot}78$

allow exact measurement of occlusion length because of severe calcification and very slow flow (velocity proximal to occlusion around 5–10 cm/s on ultrasonography). In the remaining 19 limbs it was possible to measure the length of occlusion by both methods. The correlation between the two measurements is shown in *Figure 1*.

### *Agreement over prediction of lesions suitable for percutaneous transluminal angioplasty*

A negative result by DCFI was defined as an occlusion measuring >10 cm; this would preclude treatment by angioplasty. The DCFI results compared with the angiographic assessment are shown in *Table 2*. The predictive accuracy of DCFI was calculated on the assumption that angiography provides a standard for determining lesions suitable for PTA. All patients in this study in whom angiography suggested that PTA was possible underwent a technically successful procedure. Thus for DCFI prediction the sensitivity was 94 per cent, specificity 85 per cent, positive predictive value 83 per cent, negative predictive value 94 per cent, and overall accuracy 89 per cent.

### *True negatives*

In 17 limbs DCFI demonstrated lesions not amenable to angioplasty (*Table 2*). In one of these patients, who was found to have a clinically unsuspected iliac stenosis, both tests demonstrated a normal femoropopliteal segment. Ten of the original 30 patients could have been saved unnecessary angiography had the DCFI result been used.

### *False negatives*

In one limb DCFI measured an occlusion length of 15 cm, while angiography showed it to be only 5 cm (*Table 2*). The reason for the discrepancy is unclear, but it would have resulted in the patient being denied angioplasty had DCFI alone been used.

### *False positives*

In three patients DCFI incorrectly predicted a lesion amenable to angioplasty (*Table 2*). In one, angiography showed the occlusion to be 12 cm long, compared with a DCFI measurement at the angioplasty threshold of 10 cm. In the other two limbs DCFI measured occlusions 6 and 9 cm long, compared with 5 and 8 cm, respectively, from angiography. These lesions were not suitable for angioplasty because the arterial segment proximal to the occlusions was diffusely narrowed. The actual length of dilatation required to achieve satisfactory results was therefore >10 cm; DCFI had failed to detect this.

### *True positives*

In 15 limbs DCFI correctly identified lesions that were suitable for PTA.

## Discussion

This study was restricted to patients with claudication because none required reconstructive surgery, and therefore angiography was unnecessary if a lesion was found not to be amenable to PTA. In two recent studies of DCFI screening before angioplasty[11,12], patients considered unsuitable for PTA did not proceed to angiography and the true predictive value of DCFI was therefore not determined.

Despite a small effect of magnification, arteriography overestimates occlusion length because of underfilling of the distal vessel[7]. Close agreement was found between DCFI and angiographic measurement of length in this series. There is a tendency for DCFI to overestimate occlusion length when it is small and to underestimate longer occlusions (*Figure 1*). Using the criteria in this study too few patients might proceed to angiography, with some being denied the opportunity for treatment if angiography were to show a short occlusion. Consideration should be given to raising the angioplasty threshold of duplex-measured occlusion length to 15 cm.

The primary requirement of this type of screening is a high specificity. This was achieved in this study, but with more experience the specificity may be further improved. Minimizing unnecessary angiography is important, since it is an unpleasant and uncomfortable procedure for many patients and not without risk[13].

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## Case report

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# Radiation-induced acute femoral artery thrombosis treated by thrombolysis

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Radiation damage to large arteries is only occasionally of clinical consequence. Arterial rupture, stenosis or thrombosis may occur but are usually not seen for many months or years following irradiation[1]. A case is reported of femoral artery thrombosis that occurred during external beam radiotherapy and which was treated successfully by thrombolysis.

## Case report

A 53-year-old woman undergoing pelvic irradiation for carcinoma of the anal canal was admitted with an acutely ischaemic left leg. She had received 45 Gy to the pelvis over the preceding 2 months and a 10-Gy booster dose to left inguinal metastases over the previous 9 days.

Arteriography using a contralateral femoral approach revealed a left common femoral artery occlusion (*Figure 1a*). The catheter was advanced until its tip lay in the proximal end of the occlusion and an infusion of recombinant tissue plasminogen activator (rtPA) (Boehringer–Ingelheim, Bracknell, UK) begun at 0·5 mg/h. Repeat arteriography the following day showed residual thrombus in the common femoral artery and a filling defect in the popliteal artery (*Figure 1b*). A hollow guidewire was passed through the catheter and left with its tip in the proximal end of the popliteal occlusion; rtPA infusion was continued through both the catheter and guidewire at rates of 0·5 mg/h.

Within 4 days the patient's clinical condition had resolved and the femoral arteriogram had become normal (*Figure 1c*). Conventional anticoagulation was substituted for thrombolytic therapy; radiotherapy was restarted without further incident and the patient was asymptomatic at 6-week follow-up.

## Discussion

The common femoral artery is an unusual location for acute thrombosis[2] and the sudden onset of limb ischaemia in a patient

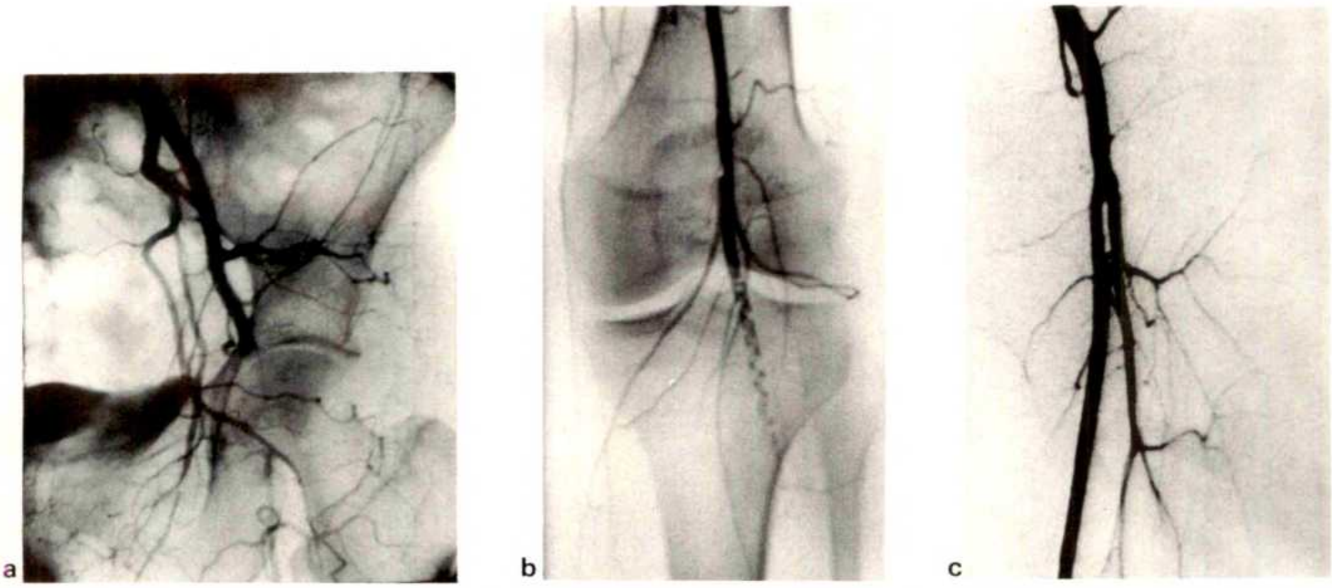

**Figure 1** **a** *Femoral angiogram showing common femoral artery obstruction.* **b** *Contrast spiralling down the popliteal artery around an intraluminal filling defect. The superficial femoral artery is normal.* **c** *Digital subtraction angiogram of the common femoral artery and its bifurcation. These appear normal following treatment; there is no evidence of external compression*

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with no previous history of arterial disease might suggest an embolus. However, no source of embolus was discovered and it was clear from superficial erythema that the common femoral artery must have been included in the radiation field. A local cause, i.e. thrombosis, was therefore considered likely.

Large arteries are relatively resistant to radiation damage and many cases of radiation-induced injury do not become apparent for several years after radiation has been received[1]. Femoral artery thrombosis has been recorded 3 years following irradiation for carcinoma of the cervix[3] and carotid artery thrombosis 1 year after irradiation to the neck[4]. The case described here is unique in that occlusive thrombosis occurred in a large artery soon after the start of radiotherapy.

Experimental evidence that may explain this early presentation is available. Fonkalsrud *et al.*[5] examined the changes in the canine femoral artery following a course of radiotherapy. Endothelial cell damage with associated fibrin and platelet deposition was seen by 48 h and was maximal at 1 week. Evidence of healing was seen by 3 weeks. Occlusive thrombosis did not occur, surprisingly, given the degree of endothelial damage. The period of maximal intimal disruption, fibrin and platelet deposition coincided with the timing of thrombosis in the present patient.

Distal emboli occurring during thrombolysis may result in a transient clinical deterioration but usually resolve with continued infusion. The popliteal occlusion was noted during the early stages of infusion, before there was significant lysis of the common femoral artery thrombosis and without any apparent deterioration of limb perfusion. This suggests that it was present at the outset and probably represented embolus from the evolving femoral thrombosis. Indeed, a distal embolus in the popliteal artery from mural thrombus in the common femoral artery may have been sufficient to reduce blood flow in the latter to the point where complete occlusion occurred.

Thrombolysis is an alternative to surgery for acute limb ischaemia[6] and was considered an attractive choice in this patient for two reasons. First, if complete lysis of clot occurred, further intervention was unlikely to be required as long as anticoagulation was continued throughout the period of intimal repair. Second, there is a danger of arterial rupture following radiation which is considerably increased by concomitant surgery[1]. Use of the contralateral femoral artery to position the angiographic catheter avoided the requirement for any interventional procedure in the area affected by radiation.

In conclusion, we recommend thrombolysis as the treatment of choice in early radiation-induced arterial thrombosis.

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# Thromboembolic prophylaxis in total hip replacement: a comparison between the low molecular weight heparinoid Lomoparan and heparin–dihydroergotamine

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*In a prospective, randomized, assessor-blind multicentre study two antithrombotic subcutaneous regimens were compared in patients undergoing total hip replacement. Group 1 (154 patients) received 750 anti-Xa units of a new low molecular weight heparinoid (Lomoparan) subcutaneously twice a day and group 2 (155 patients) received 5000 units heparin and 0·5 mg dihydroergotamine (heparin–DHE 5000) twice a day. The incidence of deep vein thrombosis, assessed by routine bilateral venography on day 10 (±1), was 17 and 32 per cent in groups 1 and 2 respectively (risk reduction 47 per cent; P = 0·007). One patient in each group developed a symptomatic pulmonary embolism confirmed by lung scanning. Major bleeding complications occurred in one patient in each group and no significant difference was observed between the two groups with respect to minor bleeding complications. Subcutaneous Lomoparan appears to be as safe as heparin–DHE 5000 at the above doses with regard to bleeding complications, and is more efficacious with respect to venous thrombosis.*

Total hip replacement without prophylaxis for venous thromboembolism is associated with an incidence of deep vein thrombosis (DVT) of about 50 per cent; fatal pulmonary embolism occurs in 1–3 per cent of patients[1,2]. In addition, DVT causes late complications such as the postphlebitic syndrome[3]. These observations show the need for efficient measures to prevent DVT after hip arthroplasty.

Among prophylactic methods evaluated by phlebography 7–12 days after surgery, low-dose heparin (5000 units two or three times a day) has been shown to be partly effective[1,2,4]. An improvement in the efficacy of prevention of DVT has been obtained by individual adjustment of heparin dose[5] or by combining heparin with dihydroergotamine (DHE)[6,7]. However, the former method is cumbersome for routine use and the latter carries the potential risk of ergotism[8].

In some recent trials with low molecular weight (LMW) heparins a further decrease of the incidence of DVT was obtained without an increase in bleeding complications[9–13]. A new LMW heparinoid (Lomoparan; Organon, Oss, the Netherlands) has recently been shown to be highly effective in orthopaedic surgery at a dose of 750 anti-Xa units administered subcutaneously twice a day[13–15]. To compare the efficacy and tolerance of Lomoparan prophylaxis with that of heparin–DHE in patients undergoing elective total hip replacement, a prospective, randomized, controlled and assessor-blind study was performed in three European orthopaedic centres

## Patients and methods

### *Patients*

In the three participating centres all consecutive patients, without age limitation, undergoing first-intention elective hip replacement between August 1986 and April 1988 were considered for entry into the study Patients were excluded for the following reasons: a history of bleeding, abnormal haemostasis tests at screening, severely abnormal liver or renal function test results, previous cerebrovascular accident, severe uncontrollable hypertension, a history of allergy to iodine-containing radiographic contrast media or to heparin, and use of drugs that interfere with haemostasis during the 8 days preceding operation In consideration of the effects of heparin–DHE treatment, patients with unstable angina pectoris, severe peripheral arterial insufficiency, or allergy to local anaesthetics were also excluded from admission to both treatment groups. Eligible patients were examined 1–3 weeks before surgery and, after giving informed consent, were randomized to either Lomoparan or heparin–DHE using the sealed envelope method. The study protocol was approved by the ethical committees of all participating centres.

### *Drugs*

The LMW heparinoid Org 10172 (Lomoparan) is a mixture of sulphated glycosaminoglycuronans with a mean molecular weight of approximately 6000 Da. It was supplied in 0·6-ml ampoules containing 750 anti-Xa units.

The heparin–DHE solution (Heparin–DHE 5000; Sandoz-Wander, Berne, Switzerland) was provided in 0·7-ml ampoules containing 5000 units sodium heparin, 0·5 mg DHE mesylate, 332 mg propylene glycol and 7·5 mg lignocaine hydrochloride monohydrate.

Patients in group 1 received 750 anti-Xa units Lomoparan and those in group 2 received 5000 units heparin–DHE per injection. In both groups the first injection was given subcutaneously 2 h before surgery, subsequently both treatments were administered twice a day until day 10 (±1) after operation.

### *Assessment for thromboembolism*

Patients had a clinical examination every day and a Doppler ultrasonographic examination on days −1, 3, 6, 9 and 10 for signs and symptoms of DVT and/or pulmonary embolism If these were present, bilateral venography and/or perfusion–ventilation lung scanning were performed without delay If thromboembolism was confirmed, the study drug was discontinued and the patient was given full-dose heparin anticoagulation. All other patients underwent bilateral venography

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between days 9 and 11 after operation. Ascending venography, using the technique of Rabinov and Paulin[16], was performed by a radiologist unaware of the treatment given For final outcome analysis, each venogram was independently evaluated by three radiologists (one from each centre) For 31 venograms (11 per cent) there were initially diverging interpretations, but joint review allowed a final consensus for all The four reliable criteria described by Rabinov and Paulin[16] were used for the diagnosis of DVT.

### *Assessment for bleeding*

Patients were examined daily for any manifestation of bleeding. Intraoperative blood loss was determined by measuring suction fluids and weighing swabs Blood loss after operation was evaluated by collecting fluids from wound drains, monitoring blood transfusion requirements, and measuring haemoglobin and haematocrit values on days −1, 2, 7 and 10

### *Follow-up*

Patients were examined clinically 4–7 weeks after the end of the study for possible late DVT or pulmonary embolism. During the follow-up period, the type and duration of anticoagulant treatment varied among centres

### *Statistical analysis*

Both an intention-to-treat analysis and an efficacy analysis were performed The former included all patients who were randomized and had an outcome assessment, including those who violated the protocol Frequencies of DVT, pulmonary embolism and haematoma, as well as the number of patients requiring blood transfusion, were compared using the $\chi^2$ test with Yates' correction Blood loss during and after operation and haemoglobin values were analysed by the Wilcoxon rank sum test

## Results

For the intention-to-treat analysis, 290 of the 309 enrolled patients were included. Nineteen patients were excluded because of missing, unilateral or uninterpretable venograms; in none was DVT diagnosed or suspected. The incidence of DVT was 17 per cent in group 1 (25 of 147) and 33 per cent in group 2 (47 of 143) ($\chi^2 = 8{\cdot}94$, 1 d.f., $P = 0{\cdot}003$)

For efficacy analysis six further patients were excluded because of protocol violation. Four patients received drugs interfering with haemostasis, one had the trial medication mixed up, and the last had venography (which was negative) performed 2 days after discontinuation of the trial medication. Of the 284 remaining patients, 145 were in group 1 (Lomoparan) and 139 in group 2 (heparin–DHE) The two treatment groups were similar with regard to demographic data, risk factors and surgical characteristics, except that the proportion of men was higher in group 1 (42 per cent) than in group 2 (29 per cent) (*Table 1*). These baseline characteristics were the result of chance.

**Table 1** *Patient details**

| | Group 1 ($n$ = 145) | Group 2 ($n$ = 139) |
|---|---|---|
| Mean(s.d.) age (years) | 66(11) | 67(11) |
| Sex ratio M:F (%) | 42:58 | 29:71† |
| Varicose veins | 43 | 43 |
| History of thromboembolic event | 12 | 13 |
| Malignant disease | 1 | 0 |
| Cardiac insufficiency | 5 | 10 |
| Anaesthesia | | |
| Spinal | 66 | 63 |
| General | 79 | 76 |
| Arthroplasty | | |
| Cemented | 25 | 22 |
| Non-cemented | 64 | 51 |
| Hybrid | 55 | 62 |
| Unknown | 1 | 4 |
| Mean (range) duration of operation (min) | 114 (60–295) | 108 (50–220) |

*Six patients were excluded because of protocol violation or for missing venography. †$P = 0{\cdot}03$ ($\chi^2$ test with Yates' correction)

**Table 2** *Efficacy analysis frequency and location of deep vein thrombosis**

| Anatomical site of DVT | Group 1 ($n$ = 145) | Group 2 ($n$ = 139) | Percentage of patients with DVT ($n$ = 69) | $P$† |
|---|---|---|---|---|
| Calf veins alone | 18 (12) | 35 (25) | | 0·009 |
| Calf and proximal veins | 6 (4) | 6 (4) | | n.s |
| Proximal veins alone | 1 (1) | 3 (2) | | n.s. |
| Total | 25 (17) | 44 (32) | | 0·007 |
| Operated leg only | 12 | 27 | 57 | |
| Non-operated leg only | 5 | 6 | 16 | |
| Bilateral | 8 | 11 | 28 | |
| Total | 25 | 44 | 100 | |

Values in parentheses are percentages *Determined by bilateral venography on day 10 (±1) after operation. DVT, deep vein thrombosis; n.s., not significant; †$\chi^2$ test

*Table 2* summarizes the most important efficacy data according to the sites of DVT. Patients in group 1 exhibited a significantly lower incidence of DVT than those in group 2 (risk reduction of 47 per cent; $\chi^2 = 7{\cdot}25$, 1 d.f., $P = 0{\cdot}007$). There was no difference in the incidence of DVT for men and women ($P = 0{\cdot}99$, analysis of variance).

In one of the participating centres only, small isolated 'rice corn' filling defects were found in calf perforating veins in 17 venograms (eight in group 1 and nine in group 2) These patients were not given therapeutic heparin treatment Including these filling defects in the analysis of the incidence of DVT hardly affected the final outcome, although the percentage of DVT in each group was higher: 23 per cent in group 1 and 38 per cent in group 2 ($\chi^2 = 7{\cdot}28$, 1 d.f., $P = 0{\cdot}007$).

In four patients early phlebography was performed because of a suspicion of DVT after clinical or Doppler ultrasonographic examination. Bilateral venography in these patients was negative in three and positive in one.

### *Pulmonary embolism and mortality*

Three patients in each group were suspected clinically to have pulmonary embolism. However, perfusion lung scanning was positive in only one in each group. No patient died

### *Tolerance and safety*

*Table 3* summarizes the incidence of bleeding complications, blood loss, volume of blood transfused and the number of patients requiring blood transfusion There were no significant differences observed except in the number of patients who received blood transfusion on the day of operation (149 of 153 in group 1 *versus* 136 of 150 in group 2, $\chi^2 = 4{\cdot}98$, 1 d.f., $P = 0{\cdot}03$). There was no difference between the two treatment groups in the change of haemoglobin and haematocrit values measured on days 2, 7 and 10 after operation.

Platelet counts were performed on days −1, 1, 3, 5, 7 and 10 Thrombocytopenia (defined as a platelet count $< 50 \times 10^9/l$) was not observed during the 10 days of DVT prophylaxis. Two patients treated for DVT demonstrated by venography developed thrombocytopenia 11 days (group 1) and 3 days (group 2) after initiation of full-dose heparin.

### *Follow-up*

Ninety-seven per cent of the patients who completed the study (132 in group 1 and 144 in group 2) were available for follow-up examination 4–7 weeks after venography. Two patients in group 1 and eight in group 2 developed symptoms compatible

**Table 3** *Bleeding complications, blood loss and blood transfusion*

| | Group 1 ($n = 153$) | Group 2 ($n = 150$) |
|---|---|---|
| Bleeding complications | | |
| No. of patients with major bleeding (prophylaxis interrupted) | 1 | 1 |
| No. of patients with moderate bleeding (prophylaxis continued) | 1 | 2 |
| No. of patients with minor wound haematomas and/or oozing | 83 | 79 |
| Blood loss | | |
| Median intraoperative loss (ml) | 800 (600–1200) | 800 (600–1160) |
| Median postoperative drainage loss (ml) | 760 (595–1015) | 750 (550–1020) |
| Transfusion requirement* | | |
| Median on day of operation (ml) | 900 (700–1200) | 820 (600–1200) |
| Median on postoperative days (ml) | 700 (600–1000) | 700 (600–1150) |
| No. of patients requiring blood transfusion | | |
| Day of operation | 149 | 136† |
| After operation | 50 | 41 |

Values in parentheses are interquartile ranges. * Volume of whole blood and/or two times the volume of packed cells †$P = 0·03$ ($\chi^2$ test), no other differences between the groups were significant

**Table 4** *Incidence of venographically proven deep vein thrombosis after heparin–dihydroergotamine prophylaxis in elective hip replacement**

| Reference | Year | No. of injections/day† | No. of patients | No. of DVTs |
|---|---|---|---|---|
| Stamatakis *et al.*[21] | 1977 | 3 | 50 | 9 (18) |
| Kakkar *et al.*[22] | 1979 | 3 | 50 | 10 (20) |
| Fredin *et al.*[23] | 1984 | 2 | 49 | 29 (59) |
| Fredin *et al.*[24] | 1984 | 2 | 50 | 21 (42) |
| Liedloff *et al.*[25] | 1984 | 2 | 100 | 25 (25) |
| Kakkar *et al.*[6] | 1985 | 3 | 500 | 131 (26) |
| Beisaw *et al.*[7] | 1988 | 3 | 63 | 16 (25) |
| Leyvraz *et al.*[26] | 1988 | 2 | 52 | 10 (19) |
| Total | | | 914 | 251 (27) |
| Present study* | 1991 | 2 | 139 | |
| Operated leg | | | | 38 (27) |
| Bilateral | | | | 44 (32) |

Values in parentheses are percentages DVT, deep vein thrombosis. *In most previous studies venography was unilateral or not specified as unilateral or bilateral. †One subcutaneous injection comprises 5000 units heparin and 0·5 mg dihydroergotamine

with DVT, of whom three (one in group 1 and two in group 2) had the diagnosis verified by venography. One patient in group 1 had pulmonary embolism confirmed by lung scanning and one in group 2 had clinical symptoms of pulmonary embolism (lung scanning not performed).

## Discussion

Although fixed doses of subcutaneous heparin are effective for the prevention of thromboembolism after general surgery[4,17,18], they have proven less satisfactory after hip arthroplasty[19,20]. Frequent individual adjustment of the heparin dose is, in spite of its good efficacy[5], not convenient for practical reasons. Previous studies, using prophylaxis with two or three doses per day of 5000 units subcutaneous heparin combined with 0·5 mg DHE, followed by mandatory phlebography, showed a DVT incidence of 27 per cent (*Table 4*). This is comparable to the 27 per cent of patients reported here with DVT in the operated leg alone (32 per cent if DVT in the non-operated leg is included). The relatively high incidence of contralateral and bilateral DVT in the present trial emphasizes the usefulness of performing systematic bilateral venography in studies evaluating the efficacy of DVT prophylaxis in elective hip replacement. The addition of DHE to heparin, although more efficacious than heparin alone, has never found widespread use because of its possible vasospastic effect on the arterial circulation[8].

The administration of LMW heparins and heparinoids for the prevention of thromboembolism after orthopaedic surgery has yielded encouraging results[9–13]. The incidences of total and proximal DVT in these studies vary from 10·8 to 19·4 per cent and from 2·9 to 8·0 per cent, respectively, and are similar to the results obtained with twice-daily administration of 750 units Lomoparan obtained in the present study (17 and 5 per cent, respectively). It is noteworthy that the incidence of proximal DVT in the group receiving heparin–DHE was already quite low at 6 per cent and comparable to that obtained with the best available prophylaxis at the present time. Although pulmonary embolism is rarely fatal in isolated calf vein thrombosis, distal DVT may progress to proximal DVT. For this reason we believe that the observed decrease in isolated calf vein thrombosis from 25 per cent in the heparin–DHE group to 12 per cent in the Lomoparan group is of potential benefit to the patient.

Except for minor variations in venographic techniques no clear explanation can be provided for the occurrence of 'rice corn' size thrombi in the perforating veins of 17 patients in one of the participating centres. As the clinical significance of these small thrombi was considered to be doubtful, no heparin treatment was given and they were not included in the analysis of DVT incidence.

Comparing heparin–DHE with Lomoparan, the frequency of bleeding complications, the amount of blood loss and the transfusion requirements were similar.

It is concluded that 750 anti-Xa units Lomoparan twice daily is at least as safe as 5000 units heparin plus 0·5 mg DHE twice daily with regard to bleeding complications, but that Lomoparan is more efficacious in preventing DVT after elective total hip replacement.

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# Reduction of thrombus formation *in vivo* using a thrombolytic agent targeted at damaged endothelial cells

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*Endothelial damage in saphenous vein harvested before coronary artery and peripheral vascular surgery has been well documented. Autogenous saphenous vein grafts are subject to early thrombotic occlusion, a process that is related to injury of this endothelial monolayer. A monoclonal antibody that binds to areas of endothelial damage (P14G11) and a non-specific immunoglobulin G (IgG) have been linked to urokinase. These conjugates were investigated* in vivo *using a rat vena cava model. The P14G11–urokinase conjugate significantly reduced thrombus formation compared with controls and non-conjugated urokinase* ($P < 0·02$)*. No reduction in thrombus formation was seen with the IgG–urokinase conjugate. This shows that thrombus formation after endothelial damage in an* in vivo *model can be reduced with a targeted thrombolytic agent. Conjugates such as this may have a role in preventing early thrombotic occlusion in vein grafts.*

Autogenous saphenous vein is the most widely used conduit for both coronary and peripheral arterial revascularization[1,2]. Vein graft thrombosis occurs in 10–20 per cent of patients during the first year after coronary artery surgery[3] and a similar attrition rate has been reported in those undergoing distal arterial reconstruction[4,5]. The endothelial monolayer may be damaged during vein harvesting[6–8] and this damage is an important aetiological factor in early thrombotic occlusion[6]. The incidence of graft thrombosis occurring within months of coronary surgery may be reduced by antiplatelet and anticoagulant drugs[9], but this treatment is not without morbidity.

A monoclonal antibody that recognizes damaged endothelial cells (P14G11) has been raised in this department[10] and successfully conjugated to urokinase to produce a thrombolytic agent with action localized to areas of endothelial damage. Preliminary work has shown that this conjugate retains its specificity for damaged endothelium *in vitro* without loss of urokinase activity[11]. This paper documents the effect of the conjugate, as well as that of unconjugated urokinase and immunoglobulin G (IgG)–urokinase conjugate, on thrombus formation in a rat model.

## Materials and methods

### *Monoclonal antibody preparation and conjugation*

The technique used to raise P14G11 has been described previously[10] The original antigen was damaged pig aortic endothelial cells, but the antibody also cross-reacts with damaged human endothelial cells. It is specific for damaged cells and does not stain intact endothelium, cultured intact or damaged vascular smooth muscle cells, or fibroblasts The antibody is an IgG$_{2a}$ subtype[10].

P14G11 and IgG (I-5381; Sigma, Poole, UK) were conjugated to urokinase (human kidney cell, Sigma) by the *n*-succinimidyl-3-(2-pyridyldithio)proprionate technique of Bode *et al.*[12] After conjugation, urokinase activity was measured using the fluorimetric method of Morita *et al.*[13].

### In vivo *thrombosis model*

A rat vena cava model[11] modified from that described by Pescador *et al.*[14] was used to test the substrates *in vivo*. Wistar rats weighing 200–250 g were anaesthetized with intraperitoneal diazepam and fentanyl, and anaesthesia maintained with intravenous pentobarbitone. The abdomen was opened and a 2·5-cm segment of the vena cava dissected free. The upper end was slung just above the right renal vein; the left renal vein was ligated and the right renal vein ligated distally and slung close to the vena cava. Both the iliac veins were slung with ties. The vena cava was then mobilized and all other tributaries ligated. Using this model, it is possible to introduce test substances into the vena cava via the iliac vein and leave them in contact with the endothelium. A venotomy can then be made in the right renal vein and the test substances flushed out with saline.

After the vena cava had been prepared as described above, the endothelium was deliberately damaged by compression with soft-jaw clamps left *in situ* for 5 min. The clamps were then removed and the upper caval sling tied. The right renal and iliac vessels were occluded by tightening the slings and 0·01 ml of test substance was introduced, as described, for 15 min. The vena cava was then flushed with saline. Blood was allowed into the vessel again before the remaining slings were tied, leaving a blood-filled isolated compartment, which was left undisturbed for 30 min. After this time the animal was killed and the vena cava opened. Any thrombus formed was removed and dried on blotting paper before weighing.

The substances tested in group 1 were urokinase (200 units/ml) and P14G11–urokinase conjugate (200 units/ml urokinase activity) against a saline control; group 2 tested IgG–urokinase conjugate (200 units/ml urokinase activity) against a saline control.

Statistical analysis was performed using the Mann–Whitney *U* test.

## Results

The weights of thrombus formed in groups 1 and 2 are shown in *Figures 1* and *2* respectively. The mean(s.e.m.) weights of

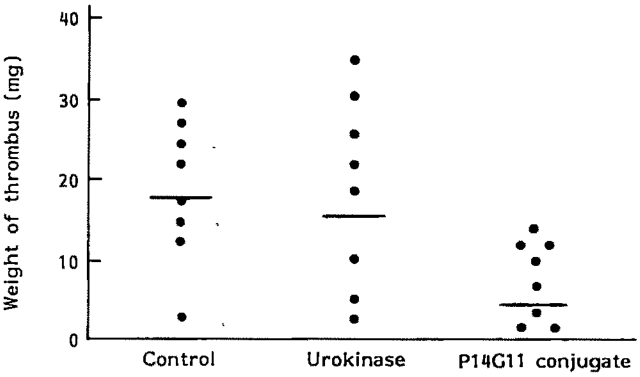

**Figure 1** *Weight of thrombus formed in group 1: control (saline)* versus *P14G11 conjugate* versus *unconjugated urokinase. Bars are means*

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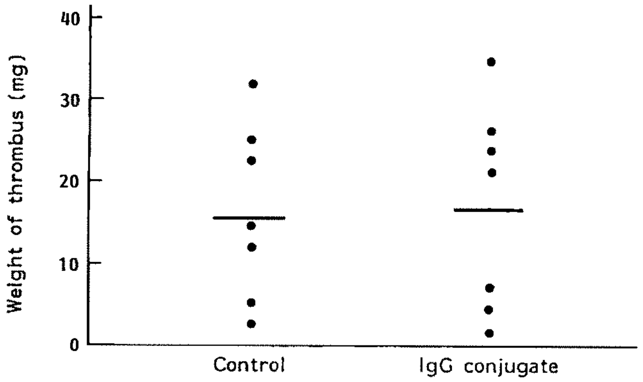

**Figure 2** *Weight of thrombus formed in group 2 control (saline)* versus *immunoglobulin G (IgG) conjugate Bars are means*

thrombus were: controls $(n = 8)$ 17·6(2·8) mg, P14G11–urokinase conjugate $(n = 8)$ 4·2(1·2) mg and unconjugated urokinase $(n = 8)$ 16·3(3·7) mg in group 1, and controls $(n = 7)$ 14·4(3·8) mg and IgG–urokinase conjugate $(n = 7)$ 16·1(4·7) mg in group 2

The P14G11–urokinase conjugate significantly reduced thrombus formation compared with the controls and unconjugated urokinase $(P < 0{\cdot}02)$. No significant difference in thrombus formation was found between the IgG–urokinase conjugate and controls $(P = 0{\cdot}70)$.

## Discussion

Early vein graft occlusion after vascular surgery seems to be related to endothelial disruption caused by surgical manipulation of the vein and its exposure to arterial haemodynamics[15,16]. The process is thrombotic in nature and platelets play a major pathogenic role[17]. Optimal surgical techniques have been described which minimize damage to the vein during its preparation[16,18–20], but some endothelial damage seems inevitable[21]. The short-term patency of coronary vein grafts would be maximized by a combination of antithrombotic therapy and careful surgical technique[16]

Antiplatelet agents such as aspirin and dipyridamole are effective in reducing the incidence of early vein graft occlusion following coronary artery surgery[22] The thrombotic process, however, begins within hours of surgery or even during the operation[23,24], and so treatment must be started before surgery or in the immediate postoperative period[25]. The administration of aspirin before operation carries an increased risk of bleeding after surgery[26] and this is particularly evident after cardiopulmonary bypass because extracorporeal circulation activates both platelets and the coagulation system[27] The period in which antiplatelet therapy is most effective in maintaining early vein graft patency is also the time when the patient is at most risk of haemorrhagic side-effects. A pharmacological agent is needed that will reduce the incidence of early thrombotic vein graft occlusion without causing systemic bleeding. The monoclonal antibody–urokinase conjugate described fulfils these criteria in theory.

Endothelial cells have recently been shown to possess specific receptors for high molecular weight urokinase and plasminogen[28], which provide a mechanism whereby these cells can regulate fibrinolytic function. This study has not shown any effect of unconjugated urokinase on thrombus formation, indicating that at the doses used it is not an adequate topical fibrinolytic agent on its own. Non-specific IgG is also known to bind to areas of endothelial damage[29] but the IgG–urokinase conjugate did not reduce thrombus formation in this model, presumably because of competition from native IgG for non-specific binding sites. This also suggests that binding of the P14G11–urokinase conjugate is mediated by specific antigen recognition and not by non-specific adherence. The specificity of the conjugate for damaged endothelial cells *in vitro* using cultured endothelial monolayers and a peroxidase-coupled second antibody staining technique[11] has been documented previously, and studies are in progress using conjugate labelled with fluorescein to determine the precise location of binding in this *in vivo* model. A thrombolytic agent targeted to areas of endothelial damage will fail to bind to vessels so severely damaged that the endothelial cells have all desquamated, current work is investigating antibodies to smooth muscle cells and the non-cellular components of the subendothelium with the aim of producing a mixture of antibody conjugates that will attach to the damaged vein under more extreme conditions.

In conclusion, a thrombolytic agent can be targeted to areas of endothelial damage and reduces thrombus formation in an *in vivo* model. Further work needs to be done to investigate the systemic effects of such a conjugate, document its persistence in the vessel wall, and assess its effect on early vein graft occlusion rates. Such an agent may have a role in preventing local thrombosis following both coronary artery and peripheral vascular surgery.

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# Recombinant basic fibroblast growth factor in red blood cell ghosts accelerates incisional wound healing

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*The pharmacological manipulation of wound healing with locally applied growth factors is now a practical possibility. The effect of topical applications of recombinant basic fibroblast growth factor (bFGF) on the strength and cellularity of healing incisional rat skin wounds was investigated. Applications of bFGF in a simple vector (either a collagen suspension or saline) were not associated with any positive effects on wound breaking load at 7 days after injury in comparison with vector-treated control wounds; at the highest dose of 50 μg per wound, breaking loads were significantly decreased from a mean(s.e.m.) of 287(22) g/cm$^2$ in controls to 201(23) g/cm$^2$* ($P < 0{\cdot}005$). *Increasing doses of applied peptide were paralleled by increasing wound cellularity. Delay of bFGF release at the site of application was achieved by encapsulation into red blood cell ghosts. Wounds treated with bFGF in such ghosts were 50 per cent stronger than paired control wounds (388(27)* versus *256(28) g/cm$^2$,* $P < 0{\cdot}002$) *7 days after injury. Treated wounds were significantly more cellular at 4 days than paired control wounds. Topical applications of bFGF applied at the time of injury exert a positive effect on incisional wound strength only when a vector that delays release is used.*

Over the past three decades a number of peptide growth factors present in serum or tissue extracts that support the growth of cells in culture have been identified. The response to injury is characterized by rapid cellular migration, division and differentiation; modulators of such processes would be expected to play a critical role. Recombinant biotechnology allows the production of specific peptides on a large scale, permitting examination of their pharmacological effects *in vivo* and their clinical use as modulators of wound healing

An incisional skin wound healing primarily by first intention is representative of a typical surgical wound The rate of healing in such a model has traditionally been assessed by the measurement of wound breaking strength, which rapidly increases in a well defined profile as granulation tissue containing collagen is deposited. Subsequent reorganization of collagen leads to a further increase in strength. Wound strength is therefore an indirect but objective measure of the healing process[1].

Local applications of transforming growth factor beta (TGF-$\beta$)[2] and platelet-derived growth factor (PDGF)[3] in collagen suspensions accelerate the gain in strength of incisional wounds. A single application of epidermal growth factor[4] has no positive effects on wound strength but, when release at the site of application is delayed by incorporation into liposomes, positive effects on wound strength between 7 and 14 days are seen Applications of either PDGF or TGF-$\beta$ in a collagen suspension can be shown to reverse the deleterious effects of steroid therapy[5], radiotherapy[6] and cytotoxics[7] on the development of incisional wound strength.

Basic fibroblast growth factor (bFGF) is a protein of 17 000 Da molecular weight found throughout the body[8]. It is a potent angiogenic factor *in vivo*[9] and *in vitro*, and is mitogenic and chemotactic for both fibroblasts and endothelial cells[10]. New blood vessel growth and fibroblast proliferation are integral elements in the formation of granulation tissue. Injection of a blocking antibody to bFGF into a wound chamber impairs deposition of granulation tissue[11]. When incorporated in a gel within the centre of a polytetrafluoroethylene tube implanted subcutaneously in mice, bFGF increases cellular infiltration[12]. Recombinant bFGF infiltrated into healing incisional wounds on the third day after operation has been shown to accelerate the gain in strength by about 35 per cent between the fifth and seventh days[13] The present study further evaluates the effect of local applications of recombinant human bFGF applied at the time of wounding in an incisional rat skin wound model. Healing was assessed by the measurement of wound breaking load, together with the analysis of histological sections using a computerized image analysis system to provide quantitative measurements of wound cellularity.

## Materials and methods

Sprague–Dawley rats weighing between 350 and 500 g were used They were caged in groups of up to four, fed standard rat chow, and maintained on a constant day–night cycle Recombinant bFGF was a gift from Chiron, Emeryville, California, USA. Activity of growth factor *in vitro* was ensured using a simple mitogenic assay using Swiss 3T3 fibroblasts Mitogenicity was assessed by the uptake of tritiated thymidine Growth factor was applied to wounds in a number of vectors. 0·15 mol/l saline, a dilute collagen suspension (Zyderm II, Collagen Corporation, Palo Alto, California, USA) or red blood cell (RBC) ghosts

### *Wound model*

Six to eight rats were used for each variable. All experiments were conducted in a blinded manner after growth factor preparation Under anaesthesia, each rat received bilateral dorsal longitudinal paired incisions 6·0 cm in length and 1·5 cm from the midline. One incision was treated with growth factor in a particular vector; the other acted as a control and received vector alone Incisions were treated and closed individually to prevent cross-contamination. Wounds were closed with five interrupted clips (Proximate; Ethicon, Edinburgh, UK). After the animals were killed, the pelts were removed Clips were removed and, using a standard cutting instrument, paired 1-cm strips cut from both

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wounds simultaneously. Typically three sets of paired strips per animal were taken for tensiometric analysis. Paired wound biopsies were also obtained for subsequent histological studies

For tensiometric analysis, each wound strip was mounted between pneumatic clamps on an Instron (High Wycombe, UK) tensiometer. Each specimen was tested to disruption at a constant strain of 5 cm/min. A load cell was connected to a chart recorder and for each specimen a load–deformation curve produced from which the breaking load of each specimen was calculated

### *Histology*

Paired wound strips were fixed in 10 per cent formal saline for 48 h and processed together before embedding in paraffin wax. Specimens were orientated so that comparable transverse sections of a wound were obtained Sections 4 μm thick were cut from each block using a microtome and stained with haematoxylin and eosin, a Van Gieson stain, or haematoxylin alone. Computerized image analysis of haematoxylin-stained nuclei in individual sections was used to produce a quantitative comparable measure of wound cellularity. Haematoxylin-stained sections were examined with a Jeneval microscope (Carl Zeiss, Borehamwood, UK). A Hitachi KP140 solid-state camera (Joyce Loebl, Gateshead, UK) produced a black-and-white image of a section, which was fed into the video interface of a Joyce Loebl Mini Magiscan image analysis system Routines were generated using general-purpose image analysis software that enabled the automatic counting of the number of nuclei within a defined space. The field analysed consisted of a rectangular area of 10 × 2 high-power fields (HPFs) (magnification ×200). The wound centre on an individual section was identified by examining both haematoxylin–eosin and Van Gieson stained sections. The rectangular counting area was orientated so that one long side corresponded to the wound centre and one short side was orientated along the outermost layer of epidermis. As the thickness of specimens was slightly greater than ten HPFs, all the nuclei within two HPFs of the wound centre were counted. Results are expressed as cells per 20 HPFs.

### *Preparation of red blood cell ghosts*

RBC ghosts have been used by investigators in the past to delay release of drugs or proteins at a site of application *in vivo*[14]. RBC ghosts were prepared according to a previously described method[15]. The Iodogen method (Pierce Chemicals, Chester, UK) was used to iodinate bFGF. Standard pore size dialysis tubing (molecular weight cut-off 12 000 Da) was used throughout Preliminary experiments indicated that retention of iodinated peptide separated from unreacted label by dialysis membrane was 92 per cent at 3 h and 60 per cent at 1 week. A high-efficiency dialysis entrapment method was used Briefly, RBCs were washed several times in 0·15 mol/l saline and then packed. The haematocrit of the packed cell was accurately determined Packed RBCs were placed in a dialysis bag with the volume of saline containing peptide theoretically necessary to shift the haematocrit to 80 per cent. The bag was sealed and placed in a hypo-osmolar lysis solution for 2 h at 4°C It was then transferred to a sealing solution of 0·15 mol/l saline at room temperature for a further 30 min. At all stages small amounts of $^{125}$I-radiolabelled bFGF were included to assess uptake. Sealed blood cells were washed twice and the distribution of radioactivity between washings and cells used as an estimate of uptake. The mean(s.d.) uptake of bFGF from six experiments was 56(6) per cent. RBC ghosts were used within 3 h of preparation. Stored at 4°C, 42 per cent of iodinated growth factor still remained within RBC ghosts at 2 weeks

### *Experimental design*

The effects of bFGF on wound breaking load were initially examined at a number of different doses and in either collagen or saline vector at 7 days As a positive control, the effect of TGF-β (2 μg in a collagen suspension) on wound breaking load at 7 days was examined. As no positive effects on breaking load were seen with bFGF delivered in either collagen or saline vectors, delaying release of bFGF at the site of application by incorporation into resealed RBC ghosts was then examined. This was done initially at 7 days and then at 4, 12 and 21 days.

### *Statistics*

All statistical comparisons were between paired wound strips; values are expressed as mean(s.e.m.). Statistical analysis used the two-tailed Wilcoxon signed rank test. Statistical and probability values were calculated on a personal computer using a software package (Arcus Professional 1 4, Aughton, Lancs, UK)

## Results

Seven animals were killed early, two because of haematoma formation and five because of self-induced wound disruption occurring in the first 24 h after injury. Applied in either saline or a collagen suspension to wounds at doses of between 0·5 and 50 μg, bFGF did not increase mean breaking loads at 7 days in comparison with paired control incisions (*Figure 1*). At the highest dose used (50 μg bFGF in saline per wound), a significant decrease in breaking load was seen at 7 days (201(23) *versus* 287(22) g/cm$^2$, $P < 0{\cdot}005$). Wounds treated with 500 ng bFGF in collagen were less cellular than control wounds (*Figure 2*). As the dose of bFGF was increased, treated wounds became increasingly cellular in comparison with control ones (*Figure 2*); areas of highly vascularized granulation tissue were visible, sometimes disrupting the incision line. Cell types visible in wounds after 7 days were predominantly macrophages and fibroblasts. Analysis of cellular distribution within individual wounds treated with bFGF revealed that, although cellularity in the centre of the wound was comparable, higher cellular counts were seen further from the wound centre in wounds treated with growth factor compared with controls. The mean breaking load at 7 days of wounds treated with TGF-β (2 μg) in a collagen suspension was approximately 50 per cent greater than that of collagen-treated controls ($P < 0{\cdot}01$) (*Figure 3*), a result in agreement with previous publications[2,4]. No differences in cellularity were apparent between wounds treated with TGF-β and control wounds at 7 days (2440(244) *versus* 3308(450) cells per 20 HPFs).

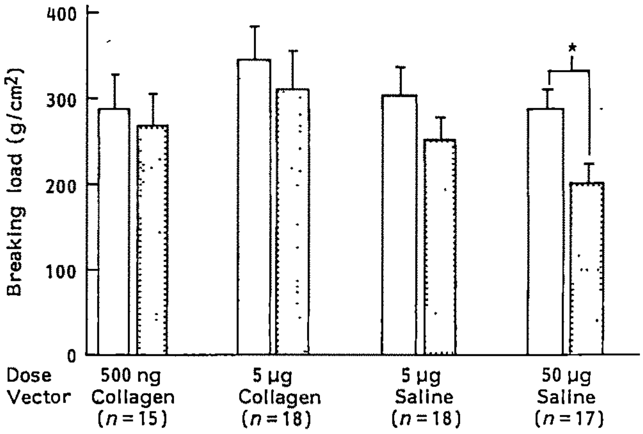

**Figure 1** *Mean(s.e m.) breaking load at 7 days of wounds treated with basic fibroblast growth factor in simple delivery vectors* □, *Control,* ▨, *treated,* n, *number of paired wound strips* *P < 0 005 (*Wilcoxon signed rank test*)

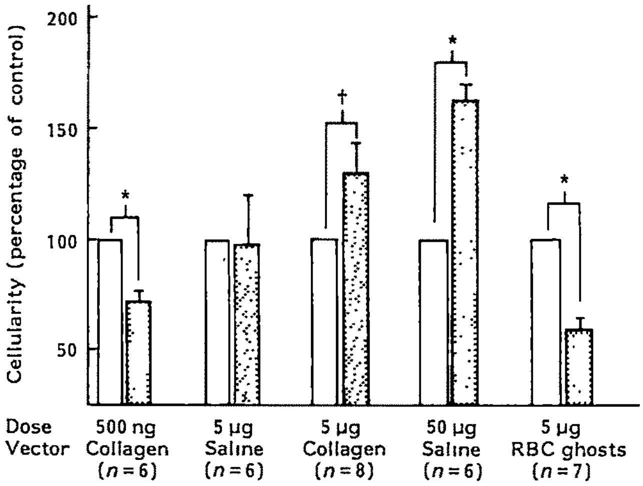

**Figure 2** *Mean(s e m.) cellularity of wounds treated with basic fibroblast growth factor expressed as a percentage of cellularity of paired control wounds.* □, *Control,* ▨, *treated,* n, *number of paired wound biopsies; RBC, red blood cell.* *P < 0 05; †P < 0·01 (*Wilcoxon signed rank test*)

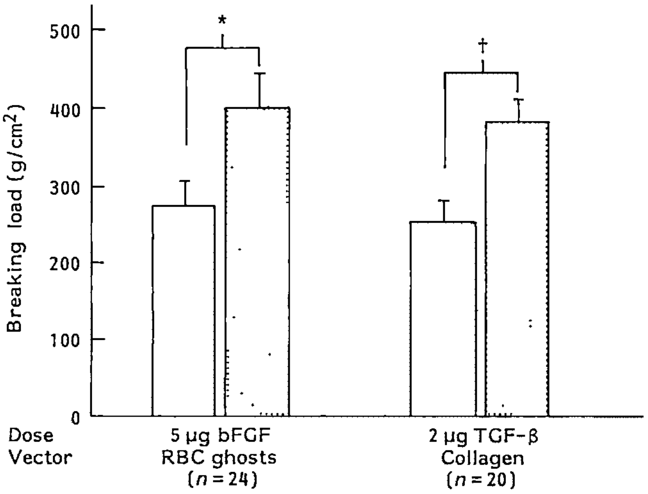

**Figure 3** *Mean(s.e.m.) breaking load at 7 days of wounds treated with basic fibroblast growth factor (bFGF) in red blood cell (RBC) ghosts or transforming growth factor beta (TGF-β) in a collagen suspension* □, *Control,* ▨, *treated,* n, *number of paired wound strips* *$P < 0{\cdot}002$, †$P < 0{\cdot}01$ *(Wilcoxon signed rank test)*

**Table 1** *Effect of 5 µg per wound basic fibroblast growth factor in red blood cell ghosts on wound breaking load at different times*

| | Wound breaking load (g/cm$^2$) | | |
|---|---|---|---|
| | Day 7 | Day 12 | Day 21 |
| Control | 256(28) | 941(49) | 1998(88) |
| Treated | 388(27) | 928(67) | 2066(117) |
| *n* | 24 | 23 | 24 |
| *P** | <0·002 | n.s. | n.s. |

Values are mean(s.e.m.). *n*, Number of paired wound strips; *Wilcoxon signed rank test

**Table 2** *Cell counts of wounds treated with basic fibroblast growth factor in red blood cell ghosts at different times*

| | Cell count (cells per 20 high-power fields) | | | |
|---|---|---|---|---|
| | Day 4 | Day 7 | Day 12 | Day 21 |
| Control | 2399(448) | 3867(412) | 3305(200) | 2556(159) |
| Treated | 3226(498) | 2260(203) | 2278(139) | 2286(155) |
| *n* | 7 | 7 | 6 | 7 |
| *P** | 0·04 | 0·015 | 0·03 | n.s. |

Values are mean(s.e.m.) *n*, Number of paired wounds, *Wilcoxon signed rank test

To delay release of bFGF at a site of application, 5 µg was encapsulated in RBC ghosts. At 7 days, wounds treated with 5 µg bFGF in such ghosts were significantly stronger than those treated with ghosts alone (388(27) *versus* 256(28) g/cm$^2$, $P < 0{\cdot}002$) (*Figure 3*), approximately a 50 per cent increase in breaking load. When RBC ghosts alone were compared with saline, no significant differences in wound breaking load were seen at 7 days (345(49) *versus* 339(55) g/cm$^2$)

At 4 days, neither control wounds nor those treated with bFGF in RBC ghosts had much intrinsic strength. Reliable testing of wound strips was found not to be possible; breaking loads were in the region of 50 g/cm$^2$. In animals killed at 12 and 21 days, no significant differences in breaking load between wounds treated with bFGF in RBC and those treated with RBC ghosts alone were seen.

At 4 days, wounds treated with bFGF in RBC ghosts were significantly more cellular than control wounds (*Table 2*). At 7 and 14 days, treated wounds were significantly less cellular than control wounds At 21 days significant differences were no longer apparent.

## Discussion

Healing by first intention is a coordinated sequential process and may conveniently be considered in three phases: cellular infiltration (0–3 days), deposition of granulation tissue (3–10 days) and remodelling, which begins at about 10 days but lasts many months and eventually produces a strong acellular scar[16]. Injury initiates platelet degranulation and release of a number of peptides including PDGF[17] and TGF-β[18]. These peptides are chemotactic for neutrophils, macrophages and fibroblasts[19]. The cellular elements infiltrate a wound in a coordinated fashion Over the first 48 h neutrophils predominate; macrophages then appear and at about 3 days fibroblasts begin to be present in large numbers[20]. Fibroblasts synthesize the collagen and matrix required for tissue repair Even in a wound healing predominantly by first intention, the wound space will be anoxic. New blood vessel growth is required to bring oxygen and nutrients. Angiogenesis and granulation tissue formation in a wound space are interdependent processes, even in healing by first intention[21].

Both PDGF[3] and TGF-β[2] applied in simple collagen suspensions accelerate the gain in strength of treated incisions. These observations have given rise to the concept that supply of peptide at a site of injury may be a rate-limiting step in an injury healing cascade. It is unlikely that such a delivery method prolongs release more than a few hours, so topical applications of these two peptides probably augment physiological platelet degranulation[22]. Presumably these effects are mediated either by augmented chemotaxis or further growth factor production by recruited cells[22].

There are no reports of bFGF in platelets Like all members of the FGF family, bFGF binds strongly to carbohydrate moieties scattered throughout the extracellular matrix, and bound at this site is probably inactive. It is suggested that, following injury, enzymes released by infiltrating cells disrupt the extracellular matrix and liberate bFGF, thus driving the further processes of repair[23]. The synthesis of bFGF occurs in most cells in the absence of a conventional signal sequence allowing entry into the Golgi apparatus; it has been unclear how a cytosolic protein is released extracellularly Sublethal damage to endothelial cells has been shown to release cytosolic bFGF into culture supernatant[24] and suggests a novel secretory pathway that may be shared by interleukin 1β *In vitro*, bFGF is an endothelial cell[10] and fibroblast[8] mitogen, while *in vivo* it is a potent angiogenic factor[9]. Both the method of release of bFGF and the process it promotes, the formation of granulation tissue, occur after an initial chemotactic stimulus produced by platelet degranulation. This may explain why local applications of recombinant peptide during the very early phases of wounding fail to stimulate subsequent events Wounds treated with higher doses of peptide in simple delivery vectors demonstrated both decreased wound breaking load at 7 days and increased cellularity. At all doses tested, no positive effects on wound strength were apparent when either saline or collagen was used as the delivery vector. At the lowest dose used (500 ng per wound) treated wounds were significantly less cellular than control ones at 7 days, a profile similar to that seen with wounds treated with growth factor in RBC ghosts, although no positive effects on breaking load were seen

Previously, 400 ng recombinant bFGF injected on the third day after wounding has been shown[13] to exert positive effects on incisional wound strength at 7 days. RBC ghosts have been used by a number of authors in the past to slow release of cytotoxics, antimicrobials or proteins at a site of application[14]. Incorporation of bFGF into a cellular delivery vehicle may in some ways mimic the normal physiological release of bFGF following injury. When release of bFGF is slowed by incorporation into RBC ghosts, a 50 per cent increase in wound breaking load is seen at 7 days This is further support that bFGF is a critical factor involved in the formation of granulation tissue At 12 and 21 days, wounds treated with bFGF in RBC ghosts were of comparable strength to control incisions, the period of early granulation tissue formation is over, the wound space is bridged, and processes of remodelling are now occurring.

Analysis of wound cellularity demonstrated that wounds treated with bFGF in RBC ghosts were more cellular at 4 days, suggesting augmentation of cellular infiltration and division during this phase of the healing process. That treated wounds were significantly less cellular at both 7 and 12 days supports the concept that the whole profile of cellular infiltration has been altered. Computerized image analysis involving nuclear counts brings greater objectivity to the assessment of wound cellularity.

In wounds healing mostly by second intention or in those healing by first intention in which angiogenesis remains a particularly critical element, a factor that stimulates these processes should be beneficial as a topical application. The present study has demonstrated that simple applications of bFGF at the time of injury do not accelerate the gain in strength of incisional wounds healing by first intention, although profound changes in wound cellularity are seen. If release at the site of application is slowed, positive effects on wound strength are apparent at 7 days, which appear to be accompanied by an accelerated accumulation of cells during the first few days of healing. Consideration should be given to the time at which any topically applied peptide acts within the healing cascade.

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# Results of the first year of breast cancer screening in a district hospital

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*The Humberside Breast Screening Service completed 1 year of screening by October 1990; 16 534 women were invited of whom 12 832 (77·6 per cent) attended. A group of 644 women (5·0 per cent) were called for further assessment and of these 134 underwent 135 primary surgical procedures. After assessment 25 were shown before operation to have cancer. One hundred and nine women had suspicious lesions and proceeded to surgical biopsy; 50 lesions proved malignant (benign: malignant biopsy ratio 1·2:1). The 75 malignant lesions represented a prevalence of 5·8 per 1000 of the screened population. Invasive cancer >1 cm in diameter formed almost half of the malignant lesions. This service has cost £32 per woman screened or £5533 per cancer detected. The results are comparable to those of previous studies and suggest that a mammographic screening service can be successfully provided in a district hospital setting.*

Interest in mammographic screening for breast cancer increased following reports of a reduction in the mortality rate of screened populations[1,2]. The Forrest Committee recommended that screening units be established throughout the UK[3]. Some doubt has been cast on the validity of the Forrest Report but its recommendations were accepted and the Humberside Breast Screening Service was established in October 1989[4,5]. As one of the first such services set up outside a recognized teaching area it draws on the expertise available in the county's district general hospitals. This report summarizes the outcome of the first year's screening.

## Patients and methods

Two mobile mammographic units are used to screen women in North and South Humberside in a 3-year cycle. Further assessment is carried out at an assessment centre in Hull with secondary centres in Grimsby and Scunthorpe.

Films from two views (mediolateral oblique and craniocaudal) were taken to the assessment centre for processing and reporting. Reporting was carried out by one of three radiologists in sessions dedicated to screening Women with films showing suspicious lesions were invited to attend the assessment clinic

The films were re-examined by the assessment team one of the three radiologists and a consultant surgeon with sessions dedicated to screening. If necessary, further investigations were carried out to identify the nature of the mammographic abnormality. These included magnification and compression mammography, ultrasonography and stereotactic localization for fine-needle aspiration cytology (Stereotactic localization was not available in the first 6 months of screening.)

The decision to proceed to surgical biopsy or definitive treatment was made at the assessment centre Surgery was carried out at the local general hospital. Women with lesions assessed as benign were returned to the routine screening programme or, rarely, recalled for early screening after 1 year. Those treated surgically were followed up at the local hospital.

## Results

The results from October 1989 to September 1990 are summarized in *Table 1* and *Figure 1*.

A total of 134 women were referred for surgical treatment. One had bilateral lesions and two required second operations to remove missed lesions. In all, 135 lesions were treated and 75 definitively identified as malignant. The prevalence of cancer in the screened population was 5·8 per 1000. Twenty-five of the cancers were diagnosed by fine-needle aspiration cytology at the assessment centre and 50 by excision biopsy. Thirty-five (47 per cent) of the malignant lesions were palpable and all of these were invasive cancers >1 cm in diameter. One hundred and ten of those treated surgically did not have a definite diagnosis of cancer before operation but all had some index of suspicion (radiographic, cytological or clinical). Fifty of these were subsequently shown to have cancer, giving a benign: malignant ratio of 1·2:1.

The primary surgical procedure for the malignant lesions was wide local excision in 60 cases (34 after radiographic localization with a guidewire) and mastectomy in 15 After receipt of the full pathology report 35 women who had been treated by local excision were advised to have or chose mastectomy.

Results of histopathological examination are summarized in *Table 2* Most of the larger tumours were 1–2 cm in diameter but one measured 10 cm after excision. To date one patient has

**Table 1** *Attendance, recall rate and cancer detection at the three assessment centres*

| | Screening | | Recall for assessment | | | | |
|---|---|---|---|---|---|---|---|
| Assessment clinic | No. invited | No. attending | No. invited | No attending | Recall rate (%) | No of malignancies | Prevalence (per 100) |
| Hull | 10 363 | 7973 (76·9) | 459 | 457 | 5·7 | 52 | 0·65 |
| Scunthorpe | 3342 | 2616 (78·3) | 89 | 89 | 3·4 | 10 | 0·38 |
| Grimsby | 2829 | 2243 (79·3) | 96 | 96 | 4·3 | 13 | 0·58 |
| Total | 16 534 | 12 832 (77·6) | 644 | 642 | 5·0 | 75 | 0·58 |

Values in parentheses are percentages

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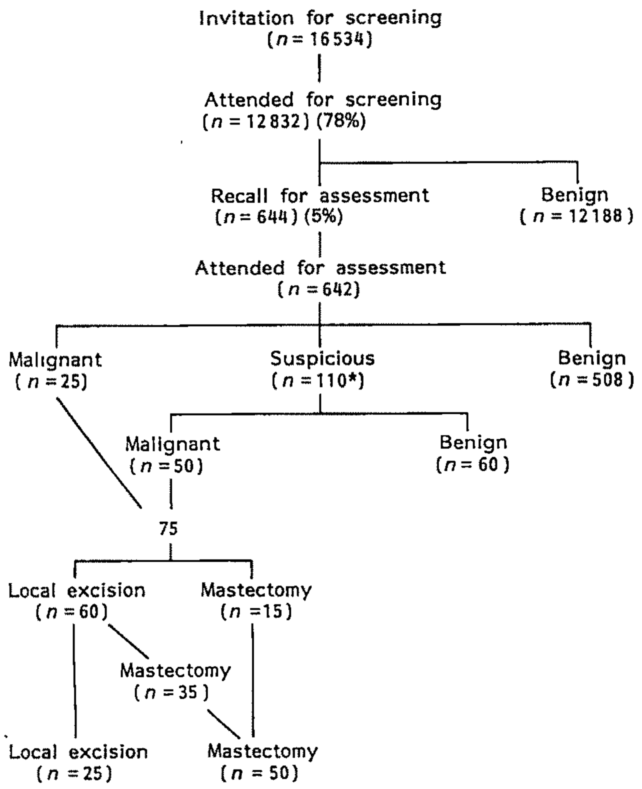

**Figure 1** *Outcome of screening. * One patient had two suspicious lesions*

**Table 2** *Histopathology of malignant lesions*

| | No. of lesions |
|---|---|
| Ductal carcinoma *in situ* | 16 (21) |
| Lobular carcinoma *in situ* | 0 (0) |
| Ductal carcinoma *in situ* with invasion | |
| <0·5 cm | 7 (9) |
| 0·5–1·0 cm | 13 (17) |
| >1·0 cm | 23 (31) |
| Lobular carcinoma *in situ* with invasion | |
| 0·5–1·0 cm | 1 (1) |
| Invasive ductal carcinoma | |
| ≤1·0 cm | 2 (3) |
| >1·0 cm | 8 (11) |
| Invasive lobular carcinoma | |
| >1·0 cm | 5 (7) |
| Total | 75 (100) |

Values in parentheses are percentages. Tumour sizes are histopathological measurements

**Table 3** *Relative performance of screening radiologists*

| | Radiologist no. | | |
|---|---|---|---|
| | 1 | 2 | 3 |
| No. reported | 5510 | 4508 | 2814 |
| No. recalled | 225 | 279 | 140 |
| Recall rate (%) | 4·1* | 6·2† | 5·0 |
| No. of cancers detected | 39 | 20 | 16 |
| Rate of detection in recalled group (%) | 17·3‡ | 7·2§ | 11·4 |

*$P < 0·001$ (1 *versus* 2, $\chi^2 = 23·01$, 1 d.f.); †$P < 0·05$ (2 *versus* 3, $\chi^2 = 4·23$, 1 d.f.), ‡$P < 0·001$ (1 *versus* 2, $\chi^2 = 12·45$, 1 d.f.), §$P$ not significant (2 *versus* 3, $\chi^2 = 2·15$, 1 d.f.)

presented with an interval cancer 8 months after screening. Review of the films showed no evidence of abnormality.

An audit of the outcome of each radiologist's decision to recall a woman for assessment is summarized in *Table 3*. Each reported films from all three centres in the screening area.

*Table 4* summarizes the surgical treatment of the 75 patients. No attempt was made to standardize treatment. The distribution of invasive and *in situ* lesions in the subgroup converted to mastectomy after local excision is shown in *Table 5*.

**Table 4** *Surgical treatment of the 75 patients with cancer*

| | Surgeon no. | | | | | |
|---|---|---|---|---|---|---|
| Treatment | 1 | 2 | 3 | 4 | 5 | Other |
| Local excision | 8 | 5 | 1 | 1 | 4 | 2 |
| Local excision plus further local clearance | 3 | 1 | 0 | 0 | 0 | 0 |
| Local excision proceeding to mastectomy | 8 | 18 | 5 | 2 | 1 | 1 |
| Primary mastectomy | 5 | 3 | 4 | 1 | 2 | 0 |
| Total | 24 | 27 | 10 | 4 | 7 | 3 |

**Table 5** *Distribution of invasive and* in situ *carcinoma in cases converted to mastectomy after local excision*

| | Surgeon no. | | | | | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | Other |
| Carcinoma *in situ* | 6 | 10 | 0 | 0 | 0 | 0 |
| Invasive carcinoma | 2 | 8 | 5 | 2 | 1 | 1 |

## Discussion

A formal publicity campaign helped to maintain an overall attendance rate of 77·6 per cent. Additional resources for publicity were used when specifically indicated, which in one instance raised an initial response rate of 50·0 per cent to 72·0 per cent.

The quality of radiology is the key to success. Two-view mammography, rather than single view as suggested in the Forrest Report, was chosen in an attempt to improve detection and reduce the recall rate. This issue is currently under review[6,7]. Recall for assessment has been as high as 10 per cent using single-view mammography while the rate reported here was 5·0 per cent. Preliminary examination of the early returns for the second year suggests that the rate has fallen to <4 per cent. The prevalence of 0·58 per 100 women screened suggests that the recall rate has been safely minimized[6,8].

The additional expense of two-view screening is partially offset by the lower recall rate and by minimizing the psychological stress that recall for assessment causes[9]. It has been suggested that screening films by two radiologists independently leads to a lower missed cancer rate[10]. The apparent difference in performance between the radiologists (*Table 3*) does lend support to double reading to reduce the number of women with benign lesions being recalled for assessment.

In the present study the benign:malignant biopsy ratio was low, reflecting the degree of prior investigation[3,8].

The use of stereotactic fine-needle aspiration cytology saved 23 patients from undergoing surgery when the lesions were radiologically uncertain. It is likely that had the stereotactic device always been operational this number would have been greater, resulting in an even lower biopsy ratio.

A cancer detection rate of 5·8 per 1000 population in a prevalent screen is in accordance with predicted levels in the UK[8]. No lobular carcinoma *in situ* was detected and it has been suggested that this is not a mammographically detectable disease[11]. The finding of 47 per cent of larger tumours is to be expected in a prevalent round. There appeared to be a difference between surgeons in their willingness to persist with conservative surgery for invasive cancer. The finding of ductal carcinoma *in situ* also seemed to influence treatment but differences were not statistically significant Mastectomy was carried out only after careful counselling. During the year only one patient was randomized into the UK trial of ductal carcinoma *in situ*, in which mastectomy is not an option. This suggests that the patient's preference influenced the choice of mastectomy. In subsequent rounds the anticipation of finding smaller lesions should lead to a lower mastectomy rate. The controversy in the management of ductal carcinoma *in situ* and the planning of surgery remains

It was calculated that for the first year the service cost approximately £32 per woman screened or £5533 per cancer detected.

This study shows that a satisfactory cancer detection rate was achieved and that screening can be successful in a district hospital setting.

## Acknowledgements

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# Assessment of non-palpable mammographic abnormalities: comparison between screening and symptomatic clinics

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*A retrospective study found that a breast screening clinic generated fewer localization biopsies for non-palpable mammographic abnormalities than a symptomatic clinic (3·36* versus *9·89 per 1000 mammograms, respectively) and that a greater proportion of such biopsies were malignant. This study determined the reason for this difference. There were 108 of 304 (35·5 per cent) and 17 of 130 (13·1 per cent) carcinomas in women attending the screening and breast clinics respectively (relative risk 2·72 (95 per cent confidence interval 1·70–4·34)). This difference was regardless of age. The characteristics of the mammographic abnormality, the Wolfe pattern, a family history of breast carcinoma, parity and age at first pregnancy were similar in both groups. Women attending the screening clinic were referred for localization biopsy after assessment by clinicians and radiologists at a joint clinic; there was no joint assessment for patients attending the breast clinic. The same staff attended both clinics, although the proportion of time spent at each varied. This study suggests that all women with a non-palpable mammographic abnormality should be reviewed at a joint assessment clinic before localization biopsy is recommended.*

The 12-year experience of 515 localization biopsies performed in 493 women with non-palpable mammographic abnormalities referred from the Edinburgh Breast Screening Clinic§ or from a symptomatic clinic where assessment included routine mammography has recently been reported[1]. The benign: malignant ratio in the two groups differed, prompting this comparative study.

## Patients and methods

A total of 515 localization biopsies were carried out on 493 women between November 1976 and December 1987. These were performed in a dedicated breast unit and all but a few after a hooked wire had been inserted under radiological control[2]. The methods and analysis have been presented in detail elsewhere[3,4].

Most women were referred from one of two sources:

1. The Edinburgh Breast Screening Clinic, to which women had been invited as part of the UK trial of early detection of breast cancer[5,6] and the Edinburgh randomized trial[6,7] Women with a suspicious non-palpable mammographic abnormality were recalled for additional mammography, clinical examination and other investigations as appropriate. The results were formally discussed at a joint review session by the screening clinic staff and radiologists; if suspicion remained, the woman returned to an assessment clinic at which a surgeon was present.
2 The symptomatic breast clinic, which reviewed 45–55 new patients each week. Before attending the clinic all women >35 years old underwent single oblique mammography and those ⩾45 years of age also had a craniocaudal view. These unreported mammograms were available to the consultant during the clinic. The clinical findings were entered on a mammographic request form and the mammograms submitted for report. Acting on this report the surgeon made the decision to undertake a localization biopsy Additional investigations were undertaken by the radiologist as required. Individual patients were discussed with the radiologist but there was no formal joint consultation or assessment clinic.

The same staff attended the symptomatic and screening clinics and all had a special interest in breast disease.

Data were stored and analysed on a database (Microsoft, Redmond, Oregon, USA) using a microcomputer (Apple, Cupertino, California, USA). Statistical analysis ($\chi^2$) was performed on Statview 512+ (Abacus Concepts, Berkeley, California, USA) software.

## Results

A total of 304 localization biopsies were performed in women referred from the screening clinic and 130 in those from the symptomatic breast clinic. The remaining 81 were performed in women referred from other sources and are not considered further.

The symptomatic clinic generated a much higher rate of biopsy (*Table 1*). The proportion of malignant biopsies per 1000 was greater in those referred from the screening clinic than the symptomatic clinic (relative risk 2·72 (95 per cent confidence interval 1·70–4·34)). The greater biopsy rate from the symptomatic breast clinic was the result of the higher rate of benign biopsies (*Table 1*).

Details of the women attending the two clinics were compared (*Table 2*). Women from the symptomatic clinic were younger and more likely to have symptoms. The number of

**Table 1** *Distribution of localization biopsies by source of referral*

| | Screening clinic | | Breast clinic | |
|---|---|---|---|---|
| | No | Biopsy rate per 1000 mammograms* | No | Biopsy rate per 1000 mammograms* |
| Biopsies | 304 | 3·36 | 130 | 9·89 |
| Malignant | 108 | 1·19 | 17 | 1·36 |
| Benign | 196 | 2·17 | 113 | 8 53 |
| Benign.malignant | 1 8 1 | | 6·6.1 | |
| Percentage of malignancies | 35·5 | | 13·1 | |

*Calculated for women attending during the period 1985–1987 and from the initial cohort of the Edinburgh Breast Screening Clinic

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§*Now the South-east Scotland Screening Clinic*

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**Table 2** *Comparison of traditional risk factors in women attending the screening and symptomatic breast clinics*

| | Screening clinic | Breast clinic |
|---|---|---|
| Mean(s d ) age at biopsy (years) | 55·2(7·1) | 49·6(9·4) |
| Mean(s d ) age at first pregnancy (years) | 26·5(5·7) | 25·0(4·2) |
| Nulliparous* | 78 (25·7) | 24 (18·5) |
| Family history of breast carcinoma* | | |
| First-degree relative | 33 (10·9) | 9 (6·9) |
| Second-degree relative | 29 (9·5) | 15 (11·5) |
| Previous contralateral carcinoma* | 2 (0·7) | 7 (5·4) |

*Values in parentheses are percentages

benign biopsies in the women from the symptomatic clinic was excessive even when stratified within 5-year age groups (*Figure 1*). There was no relationship between site of symptoms and position of mammographic abnormality: the only difference was that women attending the symptomatic clinic had a higher incidence of previous contralateral breast carcinoma, but as those with previous breast carcinoma were not recruited into the Edinburgh randomized trial this has no significance[6].

As expected, a larger proportion of women attending the screening clinic had undergone mammography previously but this did not affect the ratio of benign to malignant biopsies (*Table 3*). The mammographic features did not differ between the two clinics (*Table 4*). There was no difference between the groups in any other known risk factor.

**Table 3** *Influence of previous mammography on the benign·malignant biopsy ratio*

| | Screening clinic | | | Breast clinic | | |
|---|---|---|---|---|---|---|
| | Total | Malignant | Benign.malignant | Total | Malignant | Benign malignant |
| First mammogram | 125 | 35 (28·0) | 2·57:1 | 91 | 11 (12·1) | 7·3.1 |
| Previous mammogram | 179 | 73 (40·8) | 1·45:1 | 25 | 4 (16·0) | 5·2:1 |

Values in parentheses are percentages

**Table 4** *Mammographic indications for localization biopsy*

| | Screening clinic | Breast clinic |
|---|---|---|
| Mammographic abnormality | | |
| Microcalcification | 144 (47·4) | 46 (35·4) |
| Parenchymal disturbance | 87 (28·6) | 31 (23·8) |
| Mixed abnormality | 36 (11·8) | 12 (9·2) |
| Mammogram not traced | 37 (12·2) | 41 (31·5) |
| Wolfe parenchymal pattern | | |
| N1 | 35 (11·5) | 14 (10·8) |
| P1 | 55 (18·1) | 10 (7·7) |
| P2 | 55 (18·1) | 14 (10·8) |
| DS | 33 (10·9) | 16 (12·3) |
| DM | 18 (5·9) | 10 (7·7) |
| DY | 71 (23·4) | 25 (19·2) |
| No mammogram | 37 (12·2) | 41 (31·5) |

Values in parentheses are percentages

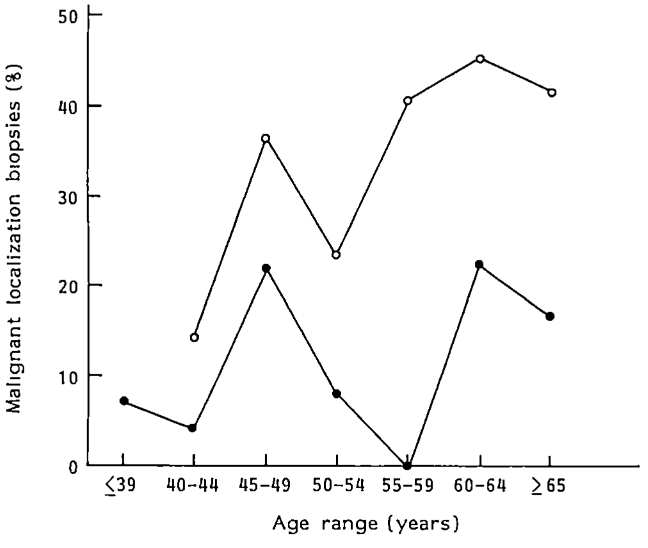

**Figure 1** *Malignant localization biopsies within each age range for women referred from screening clinic* (○) *or symptomatic clinic* (●)

## Discussion

In this study the rate of localization biopsy and the ratio of benign:malignant biopsies were significantly greater in women referred from the breast clinic than in those referred from the screening clinic. The only difference between the two groups was the manner in which the mammographic abnormality was assessed. Although the study was retrospective, the influence was so marked it is difficult to define another reason.

It is important that the number of localization biopsies is kept to a minimum, and in a well conducted screening programme the ratio of benign:malignant biopsies should not exceed 2:1. This ratio may be reduced if fine-needle stereotactic aspiration cytology is available[8]. All women, including symptomatic women found to have an incidental mammographic abnormality, should expect a similar quality of assessment, and in Edinburgh those with non-palpable mammographic abnormalities are now reviewed in a joint assessment clinic

This study has important implications for the assessment of non-palpable mammographic abnormalities The importance of a team approach involving surgeons, radiologists and screening clinic staff was emphasized by the UK Working Party[9] This study presents confirmatory evidence to support this view. Joint consultation is not usually available to symptomatic women attending as surgical outpatients or to symptomatic or screened women attending the private sector. Recently, Hall has emphasized the importance of mammographic review in reducing the number of localization biopsies[10]. The results of the present study support this view.

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## Surgical workshop

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# Disposable guarded trocar and cannula in laparoscopic surgery: a caveat

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To establish pneumoperitoneum for any form of laparoscopic surgery, the Veress needle and the first trocar and cannula are usually inserted 'blind'. Only after establishing pneumoperitoneum can the laparoscope be introduced and the remaining cannulae be inserted under direct vision.

Perforation of abdominal viscera or retroperitoneal major vessels is a well known hazard of the passage of the initial umbilical trocar. Modern laparoscopic cannulae have an external shield that shoots forward over the point of the trocar once resistance disappears (i.e. when the peritoneal cavity is entered). The use of a guarded cannula gives a much greater sense of security during this hazardous manoeuvre.

This sense of security may, however, sometimes be misplaced. In this unit a mesenteric artery was recently punctured using such a guarded cannula; it was difficult to understand how this could have happened. It was therefore decided to study the entry of a similar cannula, used in the epigastric port, when the laparoscope was available in the umbilical port. It became clear that the external guard of the disposable cannula does not shoot forward as soon as the trocar has penetrated the peritoneum but can be held back by loose peritoneum for an appreciable distance (*Figures 1* and *2*). The guard moves forwards as soon as a sufficient opening has been made in the peritoneum, but by then it is possible to have punctured an intra-abdominal structure. This situation is different from that with the Veress needle, when the blunt probe is inside the penetrating needle and therefore cannot be held back by anything once the latter has penetrated the peritoneum.

To prevent inadvertent injury while inserting the first cannula blindly, we would therefore suggest the following:

1. The potential hold-up of the safety shield should be appreciated by all surgeons using this type of trocar–cannula for laparoscopy.
2. The first trocar should not be inserted until adequate pneumoperitoneum has been achieved (at least 3·5 litres).
3. Full muscle relaxation should be present. It is not uncommon for relaxant to be wearing off at about the time at which the cannulae are inserted owing to the long time spent setting up the equipment. If relaxation is not optimal it will be more difficult to lift up the abdominal wall, and the intraperitoneal pressure will rise, preventing optimal insufflation.
4. The anterior abdominal wall should be lifted up well away from the underlying tissues, and the cannula should be inserted by rotating it slowly as it is pushed through. This manoeuvre helps to enlarge the opening in the peritoneum.
5. Subsequent cannulae, whether disposable or reusable, should be inserted under direct vision.
6. In spite of their drawbacks, guarded disposable cannulae are at present the most suitable for the first blind puncture.
7. Should the surgeon be unhappy about blind puncture of the peritoneum, then Hasson's open technique using a blunt trocar and specially adapted cannula remains the safest way of establishing pneumoperitoneum[1].

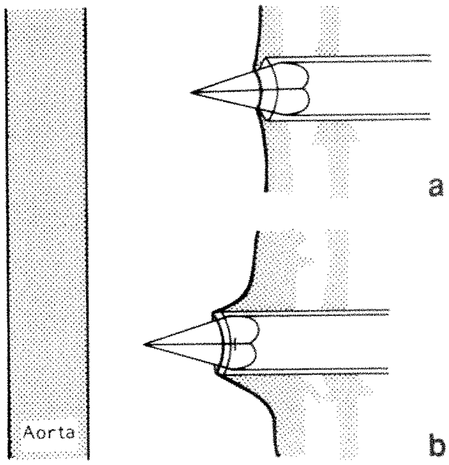

**Figure 1** *Schematic diagram illustrating the dangers of puncturing retroperitoneal vessels as the safety shield of the cannula is held back by the peritoneum.* **a** *The trocar pierces the peritoneum;* **b** *the peritoneum and extraperitoneal tissues hold up the protective shield*

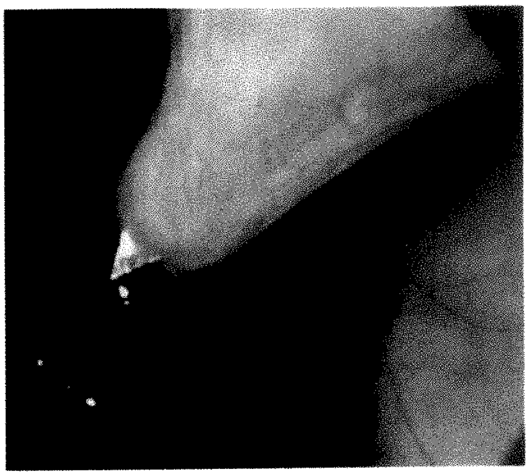

**Figure 2** *Video print showing the trocar point of a disposable cannula 3 cm into the peritoneal cavity with the safety shield held back*

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# Smoking predisposes to parotid adenolymphoma

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*Of 574 patients with previously untreated, unremarkable parotid lumps, 194 proved to have pleomorphic adenomas and 73 adenolymphomas. ABO blood group details were available in 59 and 85 per cent of patients respectively. Smoking details were available in 84 per cent of a randomly chosen 46 per cent subgroup of patients with pleomorphic adenomas and in 86 per cent of all those with adenolymphomas. The incidences of smoking and of the ABO blood groups in these two diagnoses were compared with standard sources. There was no evidence that either histological diagnosis of parotid tumours was linked to an abnormal pattern of ABO blood groups. However, there was a much greater incidence of smoking among the adenolymphoma than in the pleomorphic adenoma group: only one of 63 patients with adenolymphoma as opposed to 31 of 75 with pleomorphic adenoma had never smoked, while the mean number of cigarettes smoked by each patient with an adenolymphoma was estimated to be 300 000 as opposed to 80 000 for those with pleomorphic adenoma.*

An association has been suggested between cigarette smoking and parotid adenolymphoma[1], and this has been implicated in the apparently increasing incidence of this tumour in women[2]. In addition, several reports have suggested an association between specific parotid tumours and certain of the ABO blood groups, in particular[3,4] that pleomorphic adenomas and adenolymphomas may be linked to blood group A.

The present paper explores whether these two associations are present in patients with parotid tumours referred to this department.

## Patients and methods

The patients studied were referred to one of the authors (M.H.) in the 24-year period from 1966 to 1989. Data were collected prospectively and entered on to index cards, subsequently being transferred to a computer database to facilitate manipulation.

A total of 574 patients with previously untreated, unremarkable, parotid lumps were treated by the department's usual method of formal parotidectomy. On histological examination it was found that 73 were adenolymphomas and 194 pleomorphic adenomas. From the database, blood group details were available for 85 and 59 per cent of the patients respectively.

The medical records of all the patients with adenolymphoma were examined, as were 46 per cent of those of the pleomorphic adenoma group, these being randomly selected from the group on the basis of their hospital number. From these medical records smoking details were extracted; these were available in 86 and 84 per cent of the adenolymphoma and pleomorphic adenoma groups respectively.

Patients were categorized as non-smokers, ex-smokers and current smokers, and the average number of cigarettes smoked per day and duration of smoking recorded.

Several different control groups were used. The pleomorphic adenoma group served as the initial controls. However, to eliminate age–sex bias and the possibility of associations of smoking and/or blood group with pleomorphic adenoma, other control groups were also utilized. For smoking, the figures obtained were compared with similarly age–sex stratified national census figures[5]. For blood group, data from the local regional blood transfusion centre at Edgware (where the records of 14 000 patients were available) and figures quoted for England and Wales in a standard haematological textbook[6] were used.

## Results

The mean age at presentation with adenolymphoma was 61 (range 33–78) years. There was a large male preponderance (8:1) and the tumour was bilateral in seven patients. In the control group of pleomorphic adenomas the mean age of patients was 45 years and the age range was broader (18–95 years). The sex distribution was roughly equal, and the tumour was unilateral in all cases.

The changes of incidence and the male:female ratio over successive 5-year periods for each of the two groups are shown in *Figures 1* and *2* respectively. Smoking details are shown in *Figures 3* and *4*. With the ABO blood groups there were no statistically significant differences between patients with

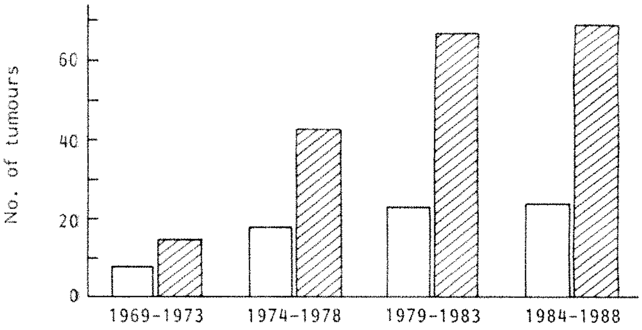

**Figure 1** *Number of adenolymphomas and pleomorphic adenomas over sequential 5-year periods.* □, *Adenolymphomas;* ▨, *pleomorphic adenomas*

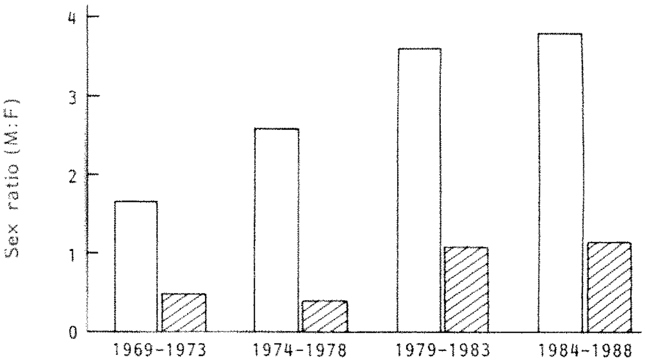

**Figure 2** *Sex ratios (M:F) over sequential 5-year periods.* □, *Adenolymphomas;* ▨, *pleomorphic adenomas*

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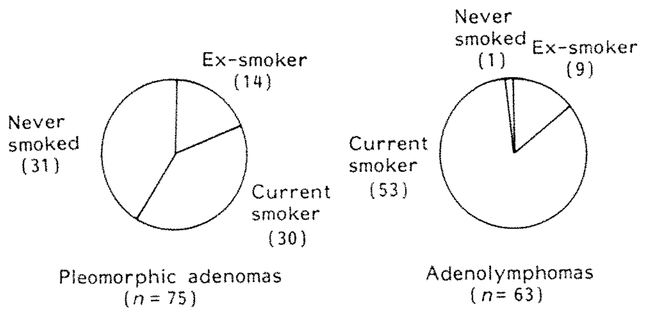

**Figure 3** *Smoking history*

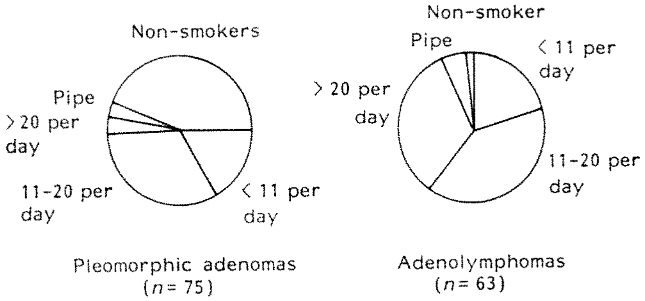

**Figure 4** *Tobacco consumption*

adenolymphoma (group O 48 per cent, A 42 per cent, B 5 per cent, AB 5 per cent), those with pleomorphic adenoma (O 51 per cent, A 36 per cent, B 9 per cent, AB 4 per cent) and patients from the Edgware transfusion centre (O 45 per cent, A 41 per cent, B 10 per cent, AB 4 per cent) ($\chi^2 = 2\cdot1$ and $2\cdot2$, 3 d.f., $P > 0\cdot5$) (*Figure 5*)

## Discussion

Since the original report[7] of parotid adenolymphoma in 1895, there have been several large retrospective reviews of this tumour[8–10]. The first large series in the UK was reported in 1986 when Ebbs and Webb described 57 patients with histologically confirmed adenolymphoma presenting over a 33-year period[1]. In this department, over a 24-year period, 73 patients with this rare tumour have been seen, making this the largest British series reported.

Previous reports have put the proportion of adenolymphoma at between 2 and 6 per cent of all parotid tumours[11]. More recent reports[2] have suggested that the figure is around 15 per cent, although the claim has been made that this tumour may now represent one-third of all parotid neoplasms[12].

The changing incidence over the study period in the present series shows that in both the adenolymphoma and pleomorphic adenoma groups there was a gradual increase in the number of patients. However, it is difficult to draw conclusions from this because, first, this department acts as a national referral centre with an undeterminable catchment population, and second, the pattern of referrals is not fixed, so that any apparent increase may not be a true one. These points probably also apply to some of the other studies reported.

What could, however, be justifiably examined is the relative incidence of adenolymphoma to pleomorphic adenoma. Overall there are always more pleomorphic adenomas, and in the present series the proportion of such adenomas was actually found to be rising. This is in contrast to previous reports[1,2].

The sex distribution remained relatively constant in the control groups, and although there was a slight female preponderance in the early years the distribution was roughly equal. In the adenolymphoma group there was always a male preponderance, which rose over the years from a 2:1 to a 4:1 ratio. This ratio is in keeping with other reports for a similar time period[10,13], although series reported in the 1950s and 1960s suggested a greater male preponderance (7:1)[8,9]. An increasing incidence in women has been previously suggested[2] and, although this cannot be confirmed in the present series, it is probably more a reflection of the small numbers involved in the early years.

An association between adenolymphoma and smoking was suggested in 1986 by Ebbs and Webb[1] and confirmed in 1987 by Lamelas *et al.*[2]. In the two groups of patients in the present study, smoking habits differed dramatically. Only one of the 63 patients with adenolymphoma had never smoked, as opposed to 31 of the 75 patients in the pleomorphic adenoma control group. This shows a clear and highly significant association of adenolymphoma with cigarette smoking ($\chi^2 = 55\cdot4$, 2 d.f., $P < 0\cdot001$). Furthermore, patients with adenolymphoma were heavier smokers than those in the pleomorphic adenoma control group, not only in that they smoked more cigarettes on average per day, but also in that they had done so for many more years. The average number of cigarettes smoked by each patient with adenolymphoma was estimated as 300 000, as opposed to 80 000 for smokers in the control group.

Albrecht and Arzt suggested in 1910 that adenolymphoma arises as a benign neoplastic change in salivary ductal inclusions in parasalivary and intrasalivary lymph nodes[14], these inclusions having been previously demonstrated by Neise in 1898 in neonates[15]. These findings were later confirmed in 1950 by Thompson and Bryant[8]. However, in 1971 Allegra[16] rejected the concept that adenolymphomas were benign neoplasms and suggested instead that they represented a manifestation of delayed hypersensitivity to metaplastic ductal epithelium, this metaplasia having arisen as a result of nutritional, metabolic or other defect. Subsequently cigarette smoke has been considered as the cause of this metaplasia[1].

The high frequency of heavy smoking in the patients in this study with adenolymphoma lends support to this theory. Additionally, all seven of the patients with bilateral tumours were heavy smokers (> 19 per day) and in the two cases in which duration had been recorded, the number of cigarettes smoked exceeded 350 000, representing a higher than average consumption even for the adenolymphoma group. The presence

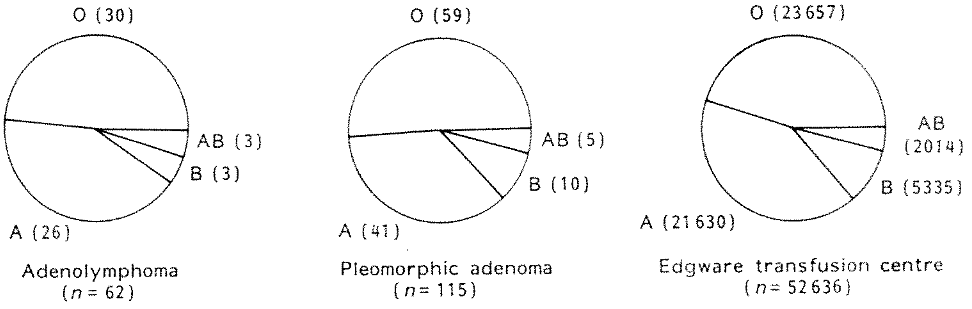

**Figure 5** *Blood group distributions*

of only one non-smoker in the adenolymphoma group is striking and leads us to advise caution in accepting the diagnosis of this tumour in a non-smoker.

Following the demonstration[17] in 1953 of an association between gastric carcinoma and blood group A, many other tumours have been investigated for similar associations. Because salivary glands secrete ABO antigenic substances, they have naturally become a focus for such investigations.

In 1958 Cameron[3] found a strong association between all salivary gland neoplasms and blood group A. He further noted a statistically significant association with parotid pleomorphic adenoma, although he could find only a non-significant trend with parotid adenolymphoma, which he attributed to the small numbers in this group. This observation was subsequently confirmed by Osbourne and De George in 1961, with ABO group A association being specifically linked to mucinous tumours (this includes both pleomorphic adenomas and adenolymphomas)[4]. However, in 1971 a further study by Garrett *et al.*[18] failed to support these findings, the authors suggesting that the previous reports may have employed unsatisfactory and non-comparable control groups and also had inappropriately grouped various histological types.

In the present study the available blood group data were examined for the two groups (pleomorphic adenomas and adenolymphomas) and no differences were found in the distribution of ABO blood groups. Neither was any difference found in the distribution when data were compared with those from a local regional blood transfusion centre, or with the overall distribution of blood groups in England and Wales. Although these two latter population control groups may not be comparable to patients with parotid lumps in the present study, they represent the best available. Therefore, no association was found between either pleomorphic adenoma or adenolymphoma and any of the ABO blood groups.

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# Surgery for primary hyperparathyroidism performed under local anaesthesia

*Patients with primary hyperparathyroidism are often elderly with cardiovascular disease and in some an operation might be hazardous owing to anaesthetic complications. A technique for operation for primary hyperparathyroidism under local anaesthesia is described. The method uses a unilateral approach. Seventeen consecutive patients operated on under local anaesthesia were compared with a group of 15 patients undergoing surgery under general anaesthesia. Normocalcaemia was achieved in 14 patients in each group. There was no difference in the extent of pain or the overall well-being between the two groups as determined by a visual analogue scale. Patients receiving local anaesthesia, however, experienced significantly less nausea after operation (P < 0·01). There was more fluctuation in blood pressure and heart rate in the general anaesthesia group compared with the other group. Surgery for primary hyperparathyroidism can be performed safely under local anaesthesia, and could be offered to patients if general anaesthesia were not suitable or involved an increased perioperative risk. It should not be recommended for routine use in patients who are fit for general anaesthesia.*

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Primary hyperparathyroidism is being diagnosed with an increasing frequency[1] and patients have lower serum calcium levels than previously[2]. The patients are usually elderly with no or only neuromuscular symptoms[3–6]. The results of surgery for primary hyperparathyroidism are excellent, with a cure rate[3,7–11] of around 90 per cent. Surgery results in a reduction of symptoms[11,12] even in patients with 'mild' disease[2,13–16]. There is a trend to operate on more mild cases than previously. Many patients with primary hyperparathyroidism are compromised by coexistent cardiovascular disease[17–20] and for some of these surgery might be hazardous owing to anaesthetic complications. Patients at high risk may be operated on safely and with acceptable results under local anaesthesia, provided that preoperative localization of the enlarged parathyroid gland(s) is obtained[21].

How is such an operation for primary hyperparathyroidism under local anaesthesia tolerated by the patient? This issue was investigated in a consecutive series of patients with the condition who were explored under local anaesthesia and compared with a group having exploration under general anaesthesia.

## Patients and methods

### *Patients*

Thirty-two consecutive patients entered the study. Seventeen were explored under local anaesthesia and 15 under general anaesthesia (one of these explorations was a reoperation because of hyperplasia). The clinical and biochemical profile of the two groups is shown in *Table 1*. No significant differences were found between the two groups.

Preoperative localization procedures in all patients included ultrasonography, thallium–technetium subtraction scintigraphy, and large vein sampling for intact parathyroid hormone (PTH). Definitive localization of an enlarged parathyroid gland was accomplished before operation if two procedures identified a lesion in the same location and/or ultrasonography with fine-needle aspiration for PTH content was positive (i.e. with a PTH concentration twice the serum PTH level) or if large venous sampling demonstrated an unequivocal unilateral gradient. In these cases, the operation was performed under local anaesthesia in patients older than 75 years with complicating diseases (cardiovascular, pulmonary or thromboembolic) and in some patients who preferred local to general anaesthesia.

### *Operation*

Patients having exploration under local anaesthesia were investigated by one surgeon (A.B.). The 15 patients explored under general anaesthesia were operated on by four different surgeons. Surgery under general anaesthesia was performed through a standard collar incision and exploration was unilateral or bilateral according to the preference of the surgeon. The dissection was always begun on the side where the preoperative localization procedures had indicated the existence of an enlarged parathyroid gland.

Patients explored under local anaesthesia underwent unilateral exposure with removal of the enlarged parathyroid gland and biopsy or excision of the other ipsilateral parathyroid gland[21].

All removed parathyroid glands were sent for frozen section, and serum samples for determination of intact PTH were obtained before and 15 min after ligation of the vascular pedicle of the enlarged parathyroid gland.

A definite diagnosis of an adenoma was based on conventional histological criteria and in most cases the intraoperative fall of serum levels of intact PTH after removal of the enlarged gland[22]. Hyperplasia was diagnosed on the basis of removal of two or more enlarged parathyroid glands.

### *Anaesthesia*

Induction of anaesthesia in the general anaesthesia group was performed by administration of thiopentone, fentanyl and pancur-

**Table 1** *Clinical and biochemical profile of the two groups of patients operated on for suspected primary hyperparathyroidism*

| | Local anaesthesia | General anaesthesia |
|---|---|---|
| Mean(s.d.) age (years) | 65(9) | 61(15) |
| Sex ratio (M:F) | 4:13 | 5:10 |
| Mean(s.d.) serum calcium (mmol/l)* | 2·79(0·22) | 2·77(0·21) |
| Mean(s.d.) serum intact parathyroid hormone (pmol/l)* | 10·5(9·1) | 11·1(10·2) |
| Mean(s.d.) serum alkaline phosphatase (units/l)* | 3·8(1·1) | 4·2(1·8) |

*Normal ranges: serum calcium 2·20–2·60 mmol/l; serum intact parathyroid hormone 1·0–5·0 pmol/l; serum alkaline phosphatase 0·8–4·6 units/l

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onium. Anaesthesia was maintained by addition of isoflurane together with incremental doses of fentanyl.

In the local anaesthesia group, no premedication was given but, at the beginning of the operation, 1–2 ml glycopyrronium bromide (0·2 mg/ml) (Robinul; A. H. Robins, Crawley, UK) was administered intravenously. During surgery, intermittent injections with 50 mg/ml pethidine hydrochloride (Petidin; Kabi Pharmacia, Solna, Sweden) and 1 mg/ml midazolam (Dormicum; Hoffman-La Roche, Basel, Switzerland) were given intravenously to supplement the local anaesthesia.

### *Postoperative care*

Patients were monitored after operation for hypocalcaemia, and therapy given if symptoms occurred. Follow-up was carried out at 8 weeks.

### *Visual analogue scale*

The patients' and nurses' opinion of overall well-being, pain and nausea were recorded on a visual 10-grade analogue scale (where 10 signified no pain, no nausea and total well-being). This was performed during operation for patients operated on under local anaesthesia and after operation (<6 h) for both groups.

### *Analysis*

Serum levels of intact PTH were measured using the commercially available N-tact PTH assay (Incstar, Stillwater, Minnesota, USA). The sensitivity of this assay is 0·13 pmol/l with an interassay variation of <11 per cent and an intra-assay variation of <6 per cent at both high and low levels. (The precision data are expressed as coefficients of variation.)

Total serum calcium values were corrected for serum albumin concentration according to the formula:

$$\mathrm{Ca_c}\ (\mathrm{mmol/l}) = \text{measured serum calcium}\ (\mathrm{mmol/l}) + 0{\cdot}02 \times [40 - \text{serum albumin}\ (\mathrm{g/l})]$$

Blood glucose levels were determined with the glucose oxidase technique.

Serum levels of alkaline phosphatase were determined by routine autoanalysis.

**Table 2** *Results from the operations in the two groups of patients*

| | Local anaesthesia | General anaesthesia |
|---|---|---|
| Mean(s.d.) operation time (min)* | 85(30) | 122(35) |
| Mean(s.d.) weight of excised enlarged parathyroid gland (g) | 1·10(1·28)<br>($n$ = 16) | 0·93(0·60)<br>($n$ = 14) |
| No. of patients with normocalcaemia at 8 weeks | 14 | 14 |
| Mean(s.d.) serum $\mathrm{Ca_c}$ at 8 weeks after operation (mmol/l) | 2·32(0·10)<br>($n$ = 14) | 2·34(0·10)<br>($n$ = 14) |

$\mathrm{Ca_c}$, calcium concentration corrected for albumin. *Time for the surgical procedure excluding anaesthesia

### *Statistics*

Results are expressed as mean(s.d.). For statistical evaluation of differences between groups, Student's $t$ test for unpaired data and the Mann–Whitney $U$ test were used. For calculation of heart rate, blood pressure and blood glucose intragroup differences, analysis of variance (ANOVA) was performed. A probability level of $P < 0{\cdot}05$ was considered significant.

## Results

The results of surgery are shown in *Table 2*. Twenty-eight patients were found to have a solitary adenoma, three had primary hyperplasia and in one no parathyroid enlargement was found.

In the group operated on under local anaesthesia, three patients had persistent hypercalcaemia, two of whom had primary hyperplasia. The operative and clinical details of these patients are shown in *Table 3*. All three patients underwent successful re-exploration. In patient 1, a second enlarged gland (weight 300 mg) was found on the left side at re-exploration under local anaesthesia. In patient 2, dissection during the first operation was complicated by a haematoma around the lower pole of the thyroid following fine-needle aspiration for PTH. At reoperation with bilateral exploration under general anaesthesia, a second enlarged parathyroid gland was found within the thyroid on the right side. A further three parathyroid glands were biopsied. This patient had five parathyroid glands. In patient 3, localization procedures indicated enlargement of a parathyroid gland on the right side. At reoperation under local anaesthesia, a parathyroid adenoma (weight 270 mg) was found on the left side, i.e. the preoperative localization was wrong.

In the group of patients explored under general anaesthesia, one had persistent hypercalcaemia at follow-up. Four normal glands had been identified at biopsy and the reason for hypercalcaemia is not known.

There was no difference in the weight of the removed glands between the patients explored under local and general anaesthesia. In one patient, the parathyroid adenoma was found in the thyroid gland and the weight could not be estimated.

At follow-up at 8 weeks no significant difference in serum calcium levels between the two groups of patients was found. Paralysis of the recurrent laryngeal nerve did not occur.

There was no difference between the nurses' and patients' opinion of overall well-being, pain and nausea. After operation no difference with regard to pain or well-being scores was found between the two groups of patients. Patients operated on under local anaesthesia had, however, significantly less nausea ($P < 0{\cdot}01$) (*Figure 1*).

ANOVA demonstrated differences in heart rate before, during and after operation in the local anaesthesia ($P < 0{\cdot}05$) and in the general anaesthesia ($P < 0{\cdot}001$) groups of patients. Patients operated on under local anaesthesia had a significantly

**Table 3** *Intraoperative findings, results from frozen section, localization procedures and diagnosis at reoperation for the three patients explored under local anaesthesia with persistent hypercalcaemia after the primary operation*

| Patient no. | Intraoperative findings | Histology (frozen section) | Preoperative localization (prediction of procedure) | Diagnosis (reoperation) |
|---|---|---|---|---|
| 1 | Two parathyroid glands excised: one enlarged (RU) and one normally sized (RL) | Adenoma (RU), weight 160 mg<br>Normal parathyroid with signs of 'suppression' (RL) | Ultrasonography: one enlarged gland (RU)<br>Scintigraphy: one enlarged gland (RU) | Hyperplasia |
| 2 | One enlarged parathyroid gland excised (RU) | Adenoma or hyperplasia (RU), weight 140 mg | Ultrasonography with fine-needle aspiration for PTH: one enlarged gland (RU) | Hyperplasia |
| 3 | Two parathyroid glands excised: one slightly enlarged (RL) and one normally sized (RU) | Both parathyroid glands normal, weight of RL 130 mg | Venous sampling for PTH: gradient to right side<br>Scintigraphy: one enlarged gland (RL) | Adenoma |

RU, right upper; RL, right lower; PTH, parathyroid hormone

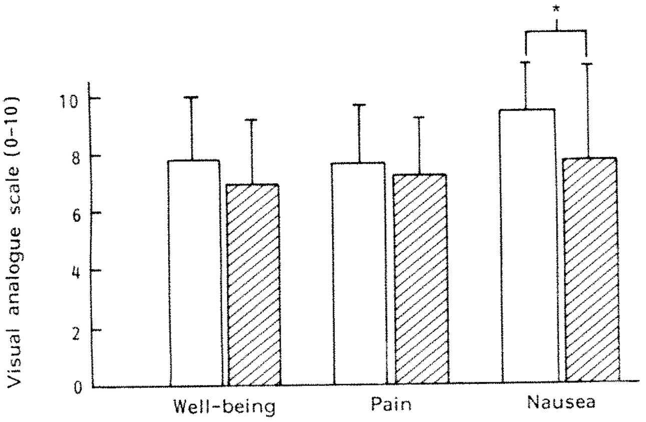

**Figure 1** *Nurse rating of well-being, pain and nausea after operation for the local anaesthesia (□) and general anaesthesia (▨) groups on a scale of 10, where 10 indicates no symptoms and total well-being. Values are mean(s.d.).* *$P < 0{\cdot}01$ *(Mann–Whitney* U *test)*

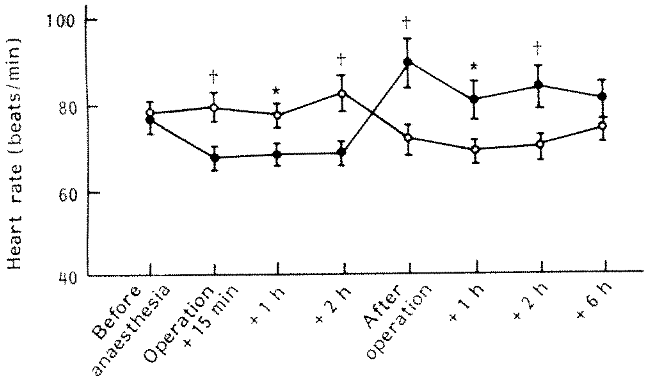

**Figure 2** *Heart rate during and after operation in the two groups of patients. Values are mean(s.d.).* ○, *Local anaesthesia;* ●, *general anaesthesia.* *$P < 0{\cdot}05$; †$P < 0{\cdot}01$ (*local* versus *general anaesthesia, Student's unpaired* t *test*)

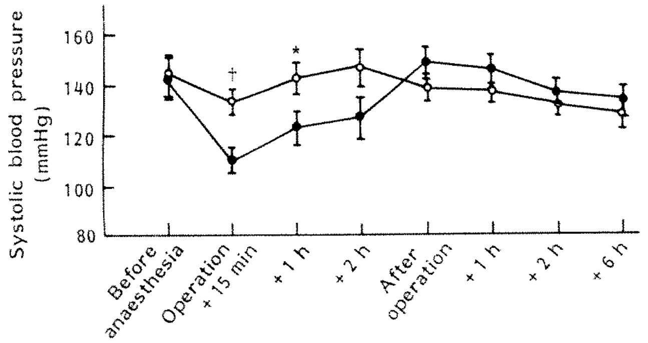

**Figure 3** *Systolic blood pressure in the two groups of patients during and after operation. Values are mean(s.d.).* ○, *Local anaesthesia;* ●, *general anaesthesia.* *$P < 0{\cdot}05$; †$P < 0{\cdot}01$ (*local* versus *general anaesthesia, Student's unpaired* t *test*)

higher heart rate during the operation compared with those undergoing surgery under general anaesthesia. Heart rate was, however, significantly higher after operation in the general anaesthesia group (*Figure 2*). The systolic blood pressure changed only in patients operated on under general anaesthesia ($P < 0{\cdot}001$). Those receiving local anaesthesia had a significantly higher systolic blood pressure during operation than those receiving general anaesthesia (*Figure 3*).

No significant differences were found in blood glucose levels within or between the groups of patients.

## Discussion

Medical follow-up[11], treatment with biphosphonates[23] and percutaneous biochemical inactivation[24] have been suggested for the management of high-risk patients with primary hyperparathyroidism. Medical follow-up and treatment with biphosphonates require close patient surveillance. Chemical parathyroidectomy yields unacceptable results and a high complication rate[24]. Surgery under local anaesthesia may be an alternative approach provided the results are adequate and the well-being of the patients acceptable. The first successful parathyroidectomy was performed under local anaesthesia by Mandl[25] in Vienna in 1925.

The present study demonstrates that patients operated on under local anaesthesia show a high degree of well-being during and after the operative procedure. The difference in intraoperative systolic blood pressure between the two groups of patients was probably due to a physiological reaction to the anaesthetic drugs given in the general anaesthesia group, since the systolic blood pressure in the local anaesthesia group did not change significantly. A significantly higher heart rate during operation compared with after surgery was evident in the patients operated on under local anaesthesia. This may indicate extra stress in this patient group. There was, however, no significant difference between the heart rate before anaesthesia and that recorded during operation.

The postoperative changes in heart rate may be of importance. To prevent myocardial ischaemia it is essential to avoid excessive changes in heart rate and blood pressure[26]. Many patients with primary hyperparathyroidism have ischaemic heart disease[19].

In terms of well-being and stress, operation under local anaesthesia seems to be at least as good as operation performed under general anaesthesia.

There were three operative failures in the local anaesthesia group, giving similar results to those in the first published series of patients operated on under local anaesthesia by Pyrtek *et al.*[21]. Incorrect preoperative localization was the major reason for surgical failure. Frozen section error contributed to the failure in one patient and a complication from ultrasonographically guided fine-needle aspiration for PTH assay in another. High sensitivity and accuracy of localization procedures are of paramount importance when performing operation for primary hyperparathyroidism under local anaesthesia.

Operation under local anaesthesia should be offered to elderly and fragile patients with primary hyperparathyroidism when operation under general anaesthesia is unsuitable. With present results the routine use of the method cannot be recommended for patients who are fit for general anaesthesia.

## Acknowledgements

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# Surgical resection for stage I cancer of the oesophagus and cardia

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*A study was carried out to establish the long-term survival of patients with stage I carcinoma of the oesophagus and cardia, and to assess the influence of various factors on the 5-year survival rate. The study, which was partly prospective and partly retrospective, involved 60 patients with early (stage I) carcinoma of the oesophagus or cardia from a total of 811 consecutive patients with such carcinomas who were referred to one regional centre over a 15-year period, 425 of whom underwent resection. Survival at 5 years was taken as the main measure of outcome. Forty-two patients (70 per cent) were alive at 5 years. None of the factors studied (sex, age, site or histological type of tumour) had a significant effect on outcome.*

According to the classification of the American Joint Committee on Cancer[1], stage I oesophageal cancers are those that involve up to 5 cm of the length of the oesophagus ($T_1$) with no extraoesophageal spread, no lymph node involvement ($N_0$), and no known distant metastases ($M_0$).

The author has been unable to find any report in Europe devoted specifically to the treatment and prognosis of stage I carcinoma of the oesophagus and cardia. This paper presents the results of a partly prospective, partly retrospective study of all patients with stage I disease treated in one regional referral centre over a 15-year period.

## Patients and methods

Between September 1970 and September 1985, 811 consecutive patients with carcinoma of the oesophagus were referred to the author. Treatment policy was always to offer resection provided there was no evidence of distant metastasis and the patient was fit for operation. Advanced age alone was not regarded as a reason for withholding surgery. Of the 811 patients, 425 (52 per cent) underwent resection of the tumour and reconstruction of the upper alimentary tract. Only 60 patients with stage I lesions were identified after clinical and pathological analysis of the resected specimens.

Apart from routine biochemical and haematological investigations, every patient underwent a radiographic contrast examination, oesophagoscopy and biopsy, bronchoscopy, and abdominal ultrasonography. Computed tomography was used once it had become available. From the results of these investigations the type and extent of resection was planned.

### *Operation*

The operation performed was a Lewis oesophagectomy with oesophagogastric anastomosis in the right chest[2] in 21 patients with a mid-thoracic tumour, and a left thoracophrenotomy[3] in 39 patients with carcinoma of the lower oesophagus and cardia. These were reconstructed by oesophagogastrectomy[4] in 36 cases, but in two patients who had undergone previous gastric surgery, and in one with suspicion of gastric invasion, total gastrectomy with Roux-en-Y oesophagojejunostomy was performed.

In all 60 stage I patients, the tumour was resected together with at least 5 cm of macroscopically normal tissue on either side. Mediastinal and coeliac lymph nodes were included in the resection. All oesophageal anastomoses were made in two layers using interrupted silk sutures, and resected specimens sent for detailed histological examination for tumour staging.

### *Postoperative follow-up*

After discharge from hospital patients were followed up at intervals of 1 month, 3 months and thereafter every 6 months for 5 years or until death. Those who survived for more than 5 years were seen annually. Patients with symptoms suggestive of recurrent tumour were admitted for investigation and palliation.

Survival was calculated by the life-table method[5]. Differences between mortality related to variables studied were analysed by Armitage's standardized normal deviate. Confidence interval (c.i.) calculations used the CIA microcomputer program (Version 1.1; British Medical Association, London, UK).

## Results

Of the 60 patients with stage I disease, there were 31 men and 29 women; the mean age was 64 (range 38–83) years. The sites and histological types of tumours are shown in *Table 1*.

The mode of presentation and symptoms on admission are shown in *Table 2*. The mean duration of symptoms before referral was 10 (range 6–16) weeks.

There were no postoperative anastomotic leaks or other serious complications.

One patient died 3 days after operation from myocardial infarction, and a second died at home 3 months after operation of bleeding from ulceration at the site of the anastomosis. The

**Table 1** *Site and histological type of 60 stage I tumours of the oesophagus and cardia*

| | Histological type | | |
|---|---|---|---|
| Site | Squamous | Adenocarcinoma | Undifferentiated |
| Mid-thoracic oesophagus | 18 (30) | 3 (5) | 0 (0) |
| Lower thoracic oesophagus and cardia | 7 (12) | 31 (52) | 1 (2) |
| Total | 25 (42) | 34 (57) | 1 (2) |

Values in parentheses are percentages

**Table 2** *Symptoms and mode of presentation in 60 patients with stage I carcinoma of the oesophagus and cardia*

| Symptom | No. of patients with main presenting symptom | No. of patients with symptom on admission |
|---|---|---|
| Dysphagia | 52 | 55 |
| Retrosternal pain or heartburn | 5 | 29 |
| Haematemesis | 2 | 4 |
| Nausea and vomiting | 1 | 4 |

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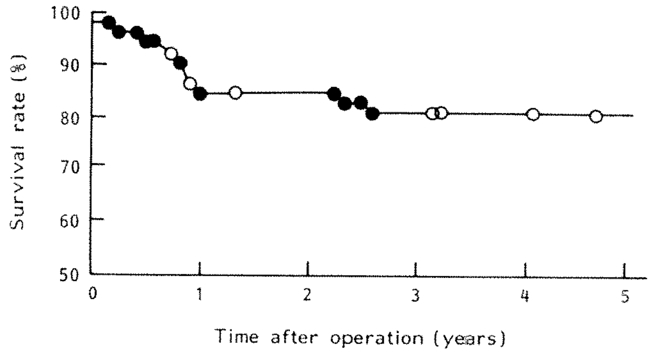

**Figure 1** *Survival curve for 60 patients undergoing operation for stage I carcinoma of the oesophagus and cardia.* ●, *Deaths from cancer;* ○, *censored deaths (those known to be unrelated to cancer)*

**Table 3** *Five-year survival rate of patients with cancer of the oesophagus and cardia: association with sex, age, site of tumour and histological type*

| Associated variables | Total | Survival at 5 years | Death within 5 years | Death in hospital |
|---|---|---|---|---|
| Sex (*n*)* | | | | |
| M | 31 | 21 (68) | 10 (32) | 0 (0) |
| F | 29 | 21 (72) | 7 (24) | 1 (3) |
| Mean (range) age (years) | 64 (38–83) | 63 (38–83) | 67 (50–81) | 78 |
| Site of tumour (*n*)* | | | | |
| Mid-thoracic | 21 | 11 (52) | 9 (43) | 1 (5) |
| Lower thoracic | 39 | 31 (79) | 8 (21) | 0 (0) |
| Histological type (*n*)* | | | | |
| Adenocarcinoma | 34 | 27 (79) | 7 (21) | 0 (0) |
| Squamous | 25 | 14 (56) | 10 (40) | 1 (4) |
| Undifferentiated | 1 | 1 (100) | 0 (0) | 0 (0) |

*Values in parentheses are percentages

actuarial survival curve is shown in *Figure 1*; 42 patients (70 per cent) were alive 5 years after operation.

The cause of death was known in 14 of the further 16 patients who died: metastatic carcinoma ($n = 7$) and debility, old age and conditions unrelated to the oesophageal cancer ($n = 7$). The influence on mortality of age, sex, site of tumour and its histological type is shown in *Table 3*.

Age and sex had no influence on survival. More patients with tumours in the lower oesophagus survived than with tumours in the mid-oesophagus ($U = 1{\cdot}89$, $P = 0{\cdot}059$; difference 27 (95 per cent c.i. 2–52) per cent). Those with adenocarcinomas (including one patient with an undifferentiated carcinoma) also had a survival advantage over those with squamous carcinoma (difference 24 (95 per cent c.i. 1–48) per cent), although the difference was not significant.

## Discussion

During the past 10–15 years there has been not only a reduction in postoperative morbidity and mortality rates among patients undergoing oesophagectomy and gastro-oesophageal reconstruction, but also improvement in the short-term survival rate[6,7]. This improvement has not, however, been matched by a corresponding overall improvement in the 5-year survival rate after resection, which remains[7] about 10 per cent.

One of the difficulties in assessing published reports is that there is little or no agreement regarding definition, amount of data reported, or method of analysis, so that even the quoted 5-year survival rate of 10 per cent loses credence. These problems include failure to indicate operability and resectability rates and exclusion of hospital mortality from discussion of long-term survival.

As a result, the role of surgery in the treatment of carcinoma of the oesophagus continues to be regarded as solely palliative by many who refer patients to specialist centres. There is, however, a subgroup of patients in whom the long-term survival rate after resection is considerably higher[7–9]. This subgroup, those with stage I cancers, merits detailed study to attempt to determine those characteristics which make the outcome in these patients so much more favourable.

All 60 patients reported here were symptomatic before diagnosis and in 52 (87 per cent) the presenting symptom was dysphagia. Endo *et al.*[10] found that most (72 per cent) of the 69 patients they described with early disease had symptoms, commonly dysphagia. These were all submucosal tumours as defined by the Japanese Society for Diseases of the Oesophagus[11]. The remainder were detected by screening or during routine follow-up for other conditions of the upper gastrointestinal tract. Therefore, most patients with stage I cancer present with dysphagia; this suggests that early oesophageal cancer can be detected without a complicated and expensive screening programme, provided those concerned in primary care are aware of it.

The incidence of early, or stage I, tumours in any surgical series of carcinoma of the oesophagus depends on the criteria used to define 'early'[11,12], the method of detection and the pattern of referral to that particular surgeon. There are difficulties of interpretation of results, however, because not all authors present their data clearly[7].

Patients with stage I cancer comprised 14 per cent of those undergoing resection in the present series, and 7 per cent of the total number referred. Using similar criteria Gatzinsky *et al.*[13] reported 14 early cancers in a total of 185 patients (8 per cent), and Hennessy and Keeling[14] found 5 per cent in a series of 239. Using the Japanese classification (in which the criteria are somewhat stricter) Huang[15] and Endo *et al.*[16] found a frequency of 3 per cent, but whatever the incidence there is no doubt that the survival rate after resection is considerably higher in patients with early cancer than in the more advanced cases.

Both the hospital mortality rate (2 per cent) and 5-year survival rate (70 per cent) in the present series compare favourably with data reported by other authors, mostly from Japan and China[9,10,17,18], who used more stringent classification criteria.

Neither age nor sex seems to have influenced long-term survival; some authors have reported better results in women, but they were concerned with overall outcome rather than just with stage I tumours[13,19–21].

The site and histological type of the tumour did not have any significant influence on long-term survival, although patients with tumours in the lower oesophagus and those with adenocarcinomas tended to do better than the others. This is contrary to results expressed by some authors[8,20] but consistent with the findings of Giuli and Gignoux[22].

In conclusion, the general pessimism towards patients with carcinoma of the oesophagus or cardia should be tempered by the knowledge that some can be cured by timely and adequate resection.

## Acknowledgements

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# Oesophageal reflex responses: abnormalities of the enteric nervous system in patients with oesophageal symptoms

*An intraluminal balloon was used to study the peristaltic reflex, which is mediated by the intrinsic nerves of the oesophagus. Serial balloon distension was performed in nine asymptomatic volunteers and 133 patients with oesophageal symptoms. Eight of the volunteers had a normal response with proximal stimulation and distal inhibition of motility. Only 42 patients (31·6 per cent) had a normal response. The commonest abnormal response (39·1 per cent) was some form of failure of the distal inhibitory reflex. Other patterns of abnormality were an unresponsive oesophagus (15·8 per cent) with no motility change during balloon inflation, or spasm (13·5 per cent) proximal to the balloon. These alterations of secondary peristaltic activity suggest that there are abnormalities of the intrinsic (enteric) nerves of the oesophagus. Different abnormalities were found in patients with similar symptoms. Awareness of this difference might allow a more rational approach to treatment. This hypothesis was tested in a small pilot study treating functional dysphagia with cisapride. Three of nine patients had marked symptomatic improvement within 4 weeks and all three had an unresponsive oesophagus. The remaining six patients, who had failure of distal inhibition or a normal response, did not improve.*

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Oesophageal manometry has heightened the awareness of oesophageal motility disorders as causes of chest pain and dysphagia. The clinical benefits of improved diagnosis have been relatively disappointing[1,2] owing, in part, to a poor understanding of the nature of the disorders identified. Achalasia and systemic sclerosis, both rare conditions, are the only motility disorders with a clearly defined pathology. The pathological basis of diffuse oesophageal spasm, nutcracker oesophagus, and common non-specific motility disorders is not clear. It is difficult to know which are true primary motility disorders, which are secondary manifestations of other oesophageal conditions, and which the result of conditions affecting other systems.

Conventional oesophageal manometry examines primary peristalsis, the initiation of which is mainly under the control of the central nervous system[3]. Secondary peristalsis is initiated and controlled by the intrinsic enteric nervous system[4], but is more difficult to study objectively. The secondary peristaltic reflex has been studied in a group of patients with common oesophageal symptoms to assess the function of the enteric nervous system and its possible relevance in the pathogenesis of oesophageal motility disorders. The working hypothesis was that there might be different abnormalities of reflex arcs in patients with similar symptoms and that awareness of these differences might facilitate a more logical approach to treatment.

## Patients and methods

### *Subjects*

Nine asymptomatic volunteers (five men, four women; median age 33 (range 25–39) years) and 133 patients (70 men, 63 women; median age 44 (range 23–79) years) were studied. The patients had a variety of oesophageal symptoms including symptomatic gastro-oesophageal reflux (32 patients), non-cardiac chest pain (45) and dysphagia (19). All patients underwent conventional oesophageal manometry, 24-h oesophageal pH recording and upper gastrointestinal endoscopy. None of the patients with dysphagia had an oesophageal stricture. The volunteers were studied by manometry only.

Nine of the above patients with dysphagia (six men, three women; median age 51 (range 35–77) years) were treated with oral cisapride (Janssen Pharmaceuticals, Wantage, UK), 10 mg three times daily. None had received any prior treatment. Clinical assessment of the severity of dysphagia was repeated after 4 weeks.

Approval for the study was obtained from the Salford District Ethical Committee. All subjects gave informed consent.

### *Oesophageal manometry*

A commercially available low-compliance six-lumen oesophageal manometry catheter with an outside diameter of 3 mm was used (Synectics Medical, Stockholm, Sweden). There were three side holes 5 cm from the catheter tip radially spaced at 120° and three further side holes at 5-cm intervals proximal to this point. The catheter was perfused with water using a low-compliance pneumohydraulic pump (Arndorfer, Greendale, Wisconsin, USA) at a rate of 0·6 ml/min. Recording channels were coupled to pressure transducers (P23ID; Gould, Leicester, UK) and to a polygraph (Grass, Quincy, Massachusetts, USA). Respiration was recorded using a nasal thermistor and the electrocardiogram monitored throughout the study period.

All medications were stopped 24 h before the test and subjects were fasted for at least 4 h. Conventional manometric recordings were made by station pull-through at 1-cm intervals. The lower oesophageal sphincter pressure was measured as previously described[5]. Relaxation of the lower sphincter was assessed and motility in the body of the oesophagus studied during a minimum of ten wet swallows of 10 ml water. Manometry records were analysed and classified using currently accepted guidelines[6].

### *Balloon stimulation*

A 3-cm long latex balloon (P. K. Morgan, Chatham, UK) was used to provide a suitable distension stimulus. Inflation with 30 ml air produced a maximum diameter of 36 mm. The balloon catheter was connected to a pressure transducer and recordings made on one channel of the polygraph.

After the completion of a conventional manometric study the balloon catheter was passed alongside the multilumen manometry

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catheter. The mid-point of the balloon was placed 10 cm above the upper margin of the lower oesophageal sphincter. One recording orifice of the manometry catheter was positioned at the same level as the balloon and there was always at least one orifice above and one below the balloon. Serial inflations of 1, 3, 5, 7, 10, 13, 15, 20, 25 and 30 ml air were performed. Inflation was rapid and sustained for at least 1 min at each volume. The balloon was rapidly and completely deflated on each occasion, and a steady baseline tracing obtained before the next inflation. Subjects could not see the process of inflation and were instructed to report any sensations experienced. The study was stopped if requested by the subject or at the discretion of the observers if there was marked discomfort. Care was taken to identify artefactual changes due to patient movement or occlusion of the recording ports by the balloon.

### *pH recording*

A standard single-channel ambulatory pH monitor with a crystal antimony electrode (Synectics) was used for 24-h pH recordings. The electrode was placed 5 cm above the lower oesophageal sphincter. Gastrosoft EsopHogram 9802 software (Version 5.10, 1987; Synectics) was used to analyse recordings according to the criteria of Johnson and DeMeester[7].

### *Statistical methods*

No assumptions were made about the distribution of the data obtained. Analysis was by non-parametric methods using $\chi^2$ and Mann–Whitney *U* tests as appropriate.

## Results

### *Manometry and pH studies*

The results of conventional manometry and prolonged pH studies are shown in *Table 1*. One volunteer had high-amplitude peristalsis ($>200$ mmHg) of prolonged duration ($>7{\cdot}5$ s) sufficient to merit the label of nutcracker oesophagus. He was confirmed as asymptomatic on repeat questioning and remains so.

**Table 1** *Results of oesophageal manometry and oesophageal pH recording*

| | Volunteers ($n = 9$) | Patients ($n = 133$) |
|---|---|---|
| Oesophageal manometry | | |
| Normal | 8 (89) | 77 (57·9) |
| Abnormal | | |
| Nutcracker oesophagus | 1 (11) | 1 (0·8) |
| Achalasia | 0 (0) | 5 (3·8) |
| Non-specific | 0 (0) | 50 (37·6) |
| Oesophageal pH recording | | |
| Normal | — | 98 (73·7) |
| Gastro-oesophageal reflux | — | 35 (26·3) |

Values in parentheses are percentages

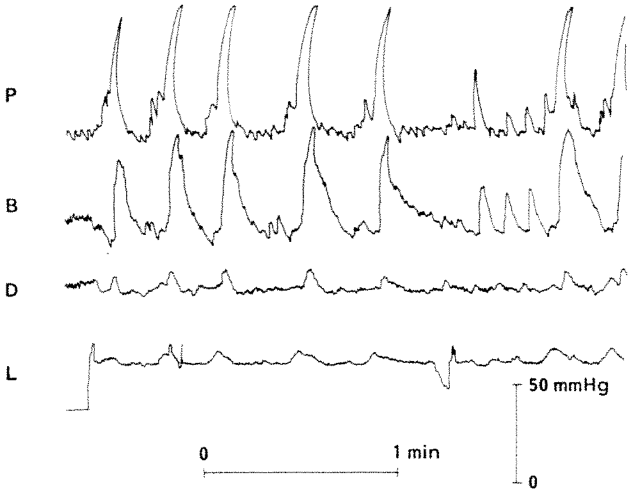

**Figure 1** *Manometric tracing showing the normal oesophageal response to intraluminal distension (B) with proximal enhancement (P) and distal inhibition (D) of contractile activity. Tracing L represents the pressure within the distending balloon*

**Table 2** *Response to distension in 133 patients*

| | No. of patients |
|---|---|
| Normal | 42 (31·6) |
| Unresponsive | 21 (15·8) |
| Failure of distal inhibition | 1 (0·8) |
| Proximal spasm and failure of distal inhibition | 22 (16·5) |
| Distal spasm | 4 (3·0) |
| Proximal and distal spasm | 25 (18·8) |
| Proximal spasm | 18 (13·5) |

Values in parentheses are percentages

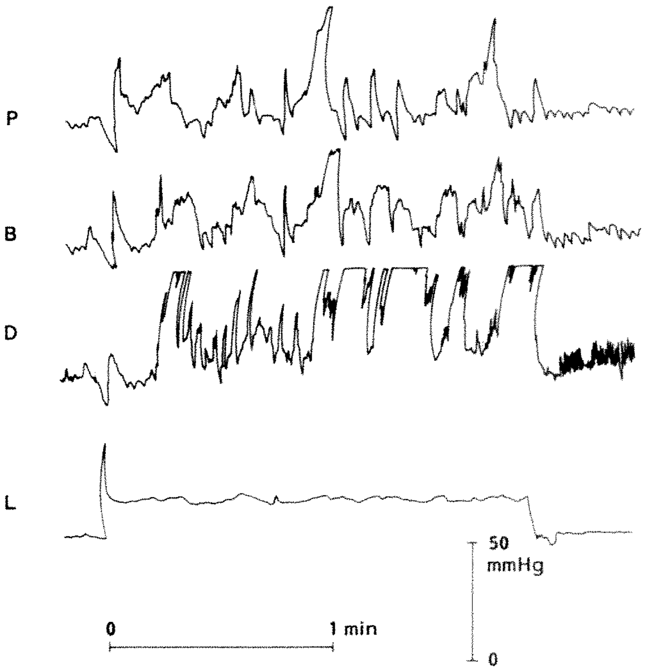

**Figure 2** *Abnormal oesophageal response to balloon distension with spasm (D) distal to the site of distension (B). Tracing P represents motility proximal to the site of distension and L represents the pressure within the distending balloon*

Fifty-six patients (42·1 per cent) had abnormalities. pH studies demonstrated gastro-oesophageal reflux in 35 (26·3 per cent), of whom 18 (51 per cent) had normal manometry.

### *Balloon stimulation*

*Volunteers.* Eight of the nine volunteers had a normal peristaltic reflex response to balloon distension with proximal enhancement and distal inhibition of motor activity (*Figure 1*). The volunteer with nutcracker oesophagus showed no motility change above or below the balloon with inflation to maximum balloon volume.

*Patients.* There was an entirely different distribution of responses in the patients (*Table 2*). Forty-two (31·6 per cent) had a normal peristaltic reflex ($\chi^2 = 9{\cdot}75$, patients *versus* volunteers, 2 d.f., $P < 0{\cdot}01$), 21 (15·8 per cent) had an unresponsive oesophagus and 70 (52·6 per cent) developed spasm or failure of inhibition of motor activity distal to the distending balloon. Spasm was considered to be present if there was a baseline pressure elevation of at least 10 mmHg with superimposed intermittent contractions (*Figure 2*). Of the 70 patients, 18 (26 per cent) with normal distal inhibition had spasm above the balloon as the only abnormality.

**Table 3** *Pattern of oesophageal response to balloon distension in 133 patients with normal and abnormal primary peristalsis*

| Response to distension | Normal peristalsis | Abnormal peristalsis |
|---|---|---|
| Normal | 29 (38) | 13 (23) |
| Spasm | 42 (55) | 28 (50) |
| Unresponsive* | 6 (8) | 15 (27) |
| Total | 77 | 56 |

Values in parentheses are percentages. $^*\chi^2 = 9{\cdot}81$, 2 d.f., $P < 0{\cdot}01$ (normal *versus* abnormal peristalsis)

**Table 4** *Symptom provocation by balloon distension*

| Diagnosis | No. of patients in whom usual symptoms reproduced |
|---|---|
| Normal motility ($n = 77$) | 48 (62) |
| Non-specific motility disorder ($n = 50$) | 25 (50) |
| Achalasia ($n = 5$) | 0 (0) |
| Nutcracker oesophagus ($n = 1$) | 1 (100) |
| Gastro-oesophageal reflux ($n = 35$) | 19 (54) |

Values in parentheses are percentages

There was no significant difference in the frequency of the various types of response between the three main presenting symptoms. There was a significant difference between those with normal and abnormal primary peristalsis; more of the latter had an unresponsive oesophagus (*Table 3*). Four of five patients with achalasia had an unresponsive oesophagus and one who did not had vigorous achalasia and developed spasm above and below the balloon. The patient with nutcracker oesophagus had a normal response to balloon distension.

*Sensations induced by distension.* Distension produced discomfort similar to the presenting symptoms in 55·6 per cent of the patients studied (*Table 4*). Retrosternal pain and heartburn were the most commonly produced symptoms. The sensation of sticking was reproduced in only seven of 55 patients who had dysphagia as part of their symptomatology.

*Effect of cisapride on functional dysphagia.* Nine of the patients with dysphagia who had not previously received any medical treatment for this symptom were given cisapride, 10 mg three times daily for 4 weeks. None had achalasia. Three had an unresponsive oesophagus and all had a dramatic and sustained symptomatic improvement. None of these three patients had a significant reduction of the amplitude of primary peristalsis on conventional manometry. Three with a normal response to distension did not improve symptomatically. The remaining three had failure of the distal inhibitory response and were unable to tolerate cisapride because of troublesome side-effects: constipation in two and severe chest pain in one.

## Discussion

The nature of most oesophageal motility disorders remains uncertain, but these studies show that the secondary peristaltic reflex is frequently abnormal in patients with a variety of oesophageal symptoms, suggesting that abnormalities of the intrinsic enteric nervous system are common.

The normal response to distension of the oesophagus has previously been described in 16 volunteers[8] and the present study confirms these findings. All asymptomatic volunteers except one demonstrated a normal response to balloon distension. One had no motility change and was found to have nutcracker oesophagus on conventional manometry. This subject was asymptomatic but may be at greater risk of developing symptoms.

Oesophageal peristalsis involves a complex and integrated interaction between central neural and peripheral myoneural control mechanisms[9]. The smooth muscle portion of the oesophagus can produce peristaltic activity without input from vagal efferent fibres[10]. Distension of the neurally isolated oesophagus *in vivo* or *in vitro* reduces muscular activity in the distal oesophagus[11,12], suggesting that the intramural enteric nervous system is responsible for the motility response to distension (secondary peristalsis). Excitation proximal to the site of distension is mediated in part by cholinergic neurones[13]. The descending inhibitory pathway is mediated by non-cholinergic, non-adrenergic neurones[14], which probably release vasoactive intestinal peptide, substance P or neuropeptide Y as the inhibitory neurotransmitter[15,16].

Secondary peristaltic activity was abnormal in more than two-thirds of the patients studied. The commonest abnormality was a failure of inhibition distal to the distending balloon, suggesting a defect in the reflex arc mediating distal inhibition.

Some patients had an unresponsive oesophagus as described by Kendall *et al.*[8], and others had spasm above the balloon as the only abnormality. This suggests the existence of different neuromuscular abnormalities, which might influence the results of treatment by pharmacological agents. It was not surprising that most of those with achalasia had an unresponsive oesophagus since degeneration of the myenteric plexus occurs in this condition. The different response in one of the patients may have been due to partial, rather than complete, denervation.

The lack of correlation between symptom complexes and specific abnormalities of the reflex arc is disappointing and may indicate that the results have no clinical significance. The few symptoms arising from the oesophagus, however, have a variety of causes and are probably the result of a series of complex neuromuscular and sensory neural interactions. The use of balloons in this oesophageal laboratory has been rationalized as the 'oesophageal tendon hammer'. An oesophageal symptom, such as dysphagia, may be associated with a variety of responses to stimulation depending on the fundamental neuromuscular abnormality. The correlation between the symptomatic improvement of functional dysphagia to cisapride and the response to balloon distension is consistent with this hypothesis. It may explain the common clinical finding that the response of patients with apparently similar oesophageal motility disorders to similar medication is unpredictable.

The concept of intrinsic neurological disorders of the oesophagus is attractive since it provides a model for future study. It is difficult to see how the concept can be validated by direct histological or histochemical study of the intrinsic nerves since suitable biopsy material is not usually available. Assessment of the response to pharmacological agents may be a useful tool for future study.

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# Case report

**Br. J. Surg. 1992, Vol. 79, September, 941**

## Thoracoabdominal oesophageal duplication

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A case of a 31-year-old man with thoracoabdominal oesophageal duplication communicating proximally and distally is reported. While alimentary tract duplication itself is not rare, communication proximally and distally in a columnar epithelial-lined oesophagus in an adult has not been previously reported.

### Case report

A 31-year-old man presented with a 2-year history of intermittent retrosternal burning pain. Results of physical examination were normal. Endoscopy of the upper gastrointestinal tract was performed, and division of the oesophagus into two lumens at 30 cm (*Figure 1*) was noted. It was possible to pass the endoscope into both lumens; both communicated with the stomach, one through a normal oesophagogastric junction and the other through an opening close to the pylorus. From 3 cm above the division both lumens were lined with columnar epithelium. Histological examination showed non-dysplastic Barrett's epithelium. A supine barium swallow showed filling of the second lumen in a posterior position. A 24-h pH profile showed significant supine reflux (12 per cent). The patient was treated with omeprazole and is symptom-free 3 months later.

### Discussion

Duplication is the term applied to lesions, either spherical or tubular, that are intimately related to the alimentary tract, are lined by mucous membrane that corresponds to any part of the alimentary tract and have a smooth muscle coat[1]. Approximately 10–20 per cent occur in the thorax[2,3]. On a review of the literature Arbona found that only six of 44 oesophageal duplications were tubular[2]. Between 2 and 4 per cent of duplications are thoracoabdominal[4], and more than 80 per cent do not communicate with the normal lumen of the alimentary tract. Most patients are diagnosed at $<1$ year of age; a very small proportion remain asymptomatic into adulthood.

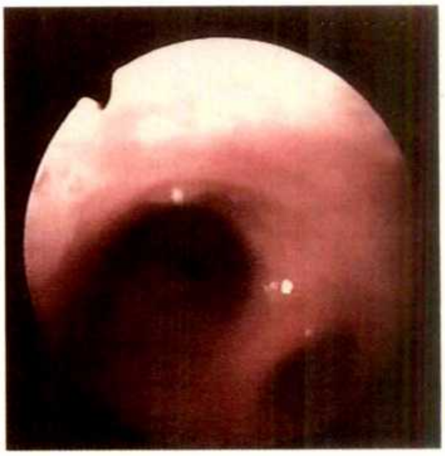

**Figure 1** *Appearance at endoscopy showing division of the oesophagus into two lumens*

In general, the presenting symptoms are due to either an enlarging mediastinal tumour compressing the respiratory and alimentary tracts or the presence of gastric mucosa in a closed cyst or blind-ending sac, which gives rise to typical peptic ulcer symptoms of pain, haemorrhage or perforation. Rarely, there have been reports of malignancy in duplications. For these reasons operation is recommended for such duplications[4,5].

Preoperative diagnosis is made using plain radiography, contrast studies and computed tomography. Results of endoscopy are generally normal, although an inward bulging of the lumen wall may be seen.

In the present patient, symptoms were due to gastro-oesophageal reflux. Endoscopic surveillance and symptomatic treatment of reflux symptoms are therefore the proposed method of management.

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**Br. J. Surg. 1992, Vol. 79, September, 942–944**

# Adequacy of paracardial dissection in subtotal *versus* total gastrectomy

*Right and left paracardial dissection represents an obligatory step in gastrectomy for gastric cancer of the lower half of the stomach because a second-level lymphadenectomy is part of the radical surgery for malignancy at this site. Whereas right and left paracardial dissection is easily accomplished during total gastrectomy, there is doubt as to whether subtotal gastrectomy achieves the same radical clearance of these groups of lymph nodes. This study therefore compared the number of lymph nodes dissected and the frequency of metastases in these compartments in 14 patients undergoing total gastrectomy and 22 submitted to subtotal gastrectomy. The mean number of lymph nodes dissected in the right paracardial compartment was 7·1 per patient undergoing total gastrectomy and 6·7 per patient in subtotal gastrectomy (P = 0·7). The mean numbers of left paracardial lymph nodes dissected in total and subtotal gastrectomy were 3·4 and 4·1 per patient respectively (P = 0·3). These data show that the same degree of radical clearance can be achieved in these nodal compartments, irrespective of the extent of gastric resection.*

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Current literature suggests that gastric cancer should be managed with subtotal resection rather than total gastrectomy[1,2], provided that a safe proximal margin is guaranteed. This would generally require a 6-cm clearance of tissue[3], although this value is somewhat dependent on the degree of tumour penetration into the gastric wall[3], the macroscopic appearance of the tumour[4,5] and the histological type according to Laurén's classification[6,7].

There is also evidence, from both Japanese[5,8–11] and German[7,12] investigations, that dissection of the second lymph node compartment could improve the prognosis; the potential benefit is being tested by ongoing trials in South Africa[13] and the UK[4].

The question is whether paracardial right and left dissections of lymph nodes, which represent the second- and third-level compartments respectively, can be performed in carcinoma of the distal third of the stomach with the same radical degree in both subtotal and total gastrectomy. The purpose of this investigation was to compare the number of lymph nodes dissected in the left and right paracardial compartments after subtotal and total gastrectomy for cancer of the lower third of the stomach, and to assess the safety of both procedures.

## Patients and methods

Thirty-six patients underwent total or subtotal gastrectomy for cancer of the lower third of the stomach. *Table 1* summarizes the main features of the series. There were 14 patients in the total gastrectomy group (six men, eight women; mean age 60·0 years) and 22 in the subtotal gastrectomy group (16 men, six women; mean age 64·0 years).

The operative procedure consisted of an upper midline incision followed by separation of the greater omentum from the transverse colon, in continuity with the upper leaflet of transverse mesocolon and peritoneum of the lesser sac investing the anterior surface of the pancreas. The infrapyloric lymph nodes were dissected after ligation of the anteroinferior pancreatic vessels. The first part of the duodenum was mobilized and transected with a GIA stapler (US Surgical, Norwalk, Connecticut, USA). The lymph nodes of the hepatico-duodenal ligament were dissected. The right gastroepiploic vessels were ligated and divided; the lymph nodes along the common hepatic artery were dissected together with those of the coeliac axis and splenic artery. The left gastric artery was ligated and divided at its origin. Lymph node dissection was carried from the coeliac axis to the right crus of the diaphragm.

To dissect the left and right paracardial nodes without carrying out a total gastrectomy, the phreno-oesophageal ligament was divided, truncal vagotomy performed, and the paracardial nodes dissected by traction on the vagi and fatty tissue surrounding the cardio-oesophageal junction (*Figure 1*). In subtotal gastrectomy it was usual to ligate and divide the first and the lowest two or three short gastric vessels, leaving the intermediate ones intact to optimize the vascular supply to the gastric stump. The stomach was then stapled just below the cardia to leave only a small fundal pouch. The gastrojejunal anastomosis along the greater curvature was carried out with an EEA stapler (US Surgical) using a 70-cm Roux-en-Y loop. The procedure was completed with dissection of the retropancreatic nodes.

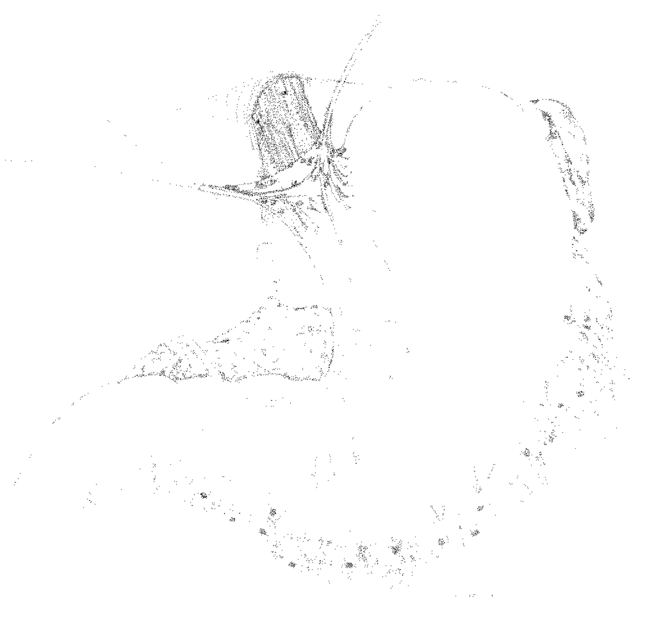

**Figure 1** *To perform adequate paracardial dissection, the phreno-oesophageal ligament just beneath the hiatus was divided. The two vagal trunks were divided, traction was applied to the vagi and all the soft tissue surrounding the cardio-oesophageal junction was dissected*

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**Table 1** *Patient details*

| Patient no | Age (years) | Histological type of adenocarcinoma | Staging | Paracardial lymph nodes | | | |
|---|---|---|---|---|---|---|---|
| | | | | Right | | Left | |
| | | | | No. resected | No. involved | No resected | No involved |
| Total gastrectomy | | | | | | | |
| 1 | 46 | Diffuse | $T_3N_2$ | 5 | 1 | 9 | 2 |
| 2 | 70 | Mucinous | $T_3N_2$ | 4 | 1 | 4 | 0 |
| 3 | 36 | Diffuse | $T_1N_0$ | 9 | 0 | 1 | 0 |
| 4 | 66 | Early | $T_2N_2$ | 6 | 4 | 1 | 1 |
| 5 | 46 | Intestinal | $T_2N_1$ | 5 | 0 | 6 | 0 |
| 6 | 67 | Diffuse | $T_3N_1$ | 13 | 0 | 3 | 0 |
| 7 | 23 | Early | $T_2N_2$ | 10 | 1 | 1 | 0 |
| 8 | 61 | Diffuse | $T_2N_1$ | 5 | 0 | 8 | 0 |
| 9 | 67 | Mucinous | $T_3N_1$ | 4 | 0 | 4 | 0 |
| 10 | 68 | Early | $T_2N_1$ | 9 | 1 | 1 | 0 |
| 11 | 79 | Diffuse | $T_1N_0$ | 8 | 0 | 1 | 0 |
| 12 | 82 | Intestinal | $T_2N_1$ | 5 | 0 | 1 | 0 |
| 13 | 50 | Early | $T_2N_1$ | 5 | 0 | 5 | 0 |
| 14 | 79 | Diffuse | $T_3N_2$ | 12 | 2 | 3 | 0 |
| Total | | | | 100 | 10 | 48 | 3 |
| Subtotal gastrectomy | | | | | | | |
| 1 | 79 | Early diffuse | $T_1N_0$ | 9 | 0 | 6 | 0 |
| 2 | 45 | Diffuse | $T_1N_0$ | 4 | 0 | 3 | 0 |
| 3 | 58 | Diffuse | $T_3N_2$ | 5 | 3 | 3 | 0 |
| 4 | 52 | Tubular | $T_2N_0$ | 2 | 0 | 3 | 0 |
| 5 | 64 | Diffuse | $T_2N_0$ | 14 | 4 | 3 | 0 |
| 6 | 67 | Intestinal | $T_2N_1$ | 4 | 0 | 3 | 0 |
| 7 | 54 | Diffuse | $T_2N_1$ | 2 | 0 | 3 | 0 |
| 8 | 70 | Mucinous | $T_3N_0$ | 4 | 0 | 4 | 0 |
| 9 | 62 | Early intestinal | $T_1N_0$ | 12 | 0 | 5 | 0 |
| 10 | 73 | Intestinal | $T_2N_2$ | 11 | 0 | 8 | 1 |
| 11 | 65 | Diffuse | $T_3N_1$ | 8 | 0 | 3 | 0 |
| 12 | 61 | Early diffuse | $T_1N_0$ | 8 | 0 | 6 | 0 |
| 13 | 25 | Diffuse | $T_2N_1$ | 3 | 0 | 3 | 0 |
| 14 | 75 | Diffuse | $T_3N_0$ | 4 | 0 | 3 | 0 |
| 15 | 54 | Tubular | $T_2N_1$ | 3 | 1 | 3 | 0 |
| 16 | 65 | Diffuse | $T_3N_1$ | 11 | 1 | 5 | 0 |
| 17 | 50 | Intestinal | $T_1N_0$ | 3 | 0 | 4 | 0 |
| 18 | 71 | Diffuse | $T_2N_2$ | 10 | 1 | 8 | 1 |
| 19 | 76 | Diffuse | $T_2N_1$ | 7 | 1 | 3 | 0 |
| 20 | 79 | Diffuse | $T_1N_0$ | 13 | 0 | 3 | 0 |
| 21 | 82 | Intestinal | $T_1N_0$ | 3 | 0 | 3 | 0 |
| 22 | 82 | Early diffuse | $T_2N_1$ | 8 | 1 | 6 | 0 |
| Total | | | | 148 | 12 | 91 | 2 |

Staging follows the tumour node metastasis (TNM) system

All the fatty areolar tissue of the left and right paracardial regions was sent separately for pathological assessment after immersion in Bouin's solution. All fragments of yellow-stained tissue >4–5 mm in size were carefully dissected and prepared for histological examination. In this way it was possible to identify the small lymph nodes; some nodules of 4–5 mm were subsequently recognized as fatty tissue

Statistical analysis of the number of resected lymph nodes was performed using Student's *t* test.

## Results

The mean operating times for total gastrectomy and subtotal gastrectomy were 202 and 208 min respectively. There were no deaths after either procedure. Patients were discharged at a mean of 12 days after both total and subtotal operations.

The mean number of lymph nodes dissected in the right paracardial compartment was 7·1 per patient for total gastrectomy and 6·7 per patient for subtotal gastrectomy (*Table 1*; $P = 0{\cdot}7$). The mean numbers of left paracardial lymph nodes dissected at total and subtotal gastrectomy were 3·4 and 4·1 per patient respectively ($P = 0{\cdot}3$). Nodal involvement of right and left paracardial compartments was present in 36 and 11 per cent of patients, respectively, and in 8 9 and 3·6 per cent of removed lymph nodes respectively.

## Discussion

There is little doubt that subtotal gastrectomy can afford the same radical clearance as total gastrectomy at lymph node level 1 and on lymph nodes along the left gastric artery, along the common hepatic artery and around the coeliac artery. However, dissection of the right and left cardial nodes may be less radical in subtotal gastrectomy because of the fear that skeletonizing the upper part of the stomach and distal oesophagus might jeopardize the vascularization. On the other hand, metastatic involvement of the right paracardial compartment in cancer of the lower third of the stomach is reported[5,10,11,14] to be in the range of 6–18 per cent, depending on the stage of the tumour, with a mean 5-year survival rate[5] of about 21 per cent. These values are less than the 36 per cent rate of nodal involvement observed in the present study and further stress the radical nature of the procedure reported.

Present data also show that in subtotal gastrectomy lymph node dissection of the right paracardial region, representing a second-level compartment in cancer of the lower third of the stomach, can be performed to the same radical degree obtained in total gastrectomy Furthermore, in subtotal gastrectomy a percentage of metastatic deposits of cancer cells within these nodes has been obtained that is higher than that reported by Japanese authors, usually regarded as meticulous in their nodal dissection. Nevertheless, the choice between subtotal and total gastrectomy should rely not on the desired extent of nodal dissection but primarily on the site of the lesion in the stomach. This is obviously valid when an extensive nodal and extranodal spread of the tumour does not exist. However, when there is such a spread, the surgeon is faced with a neoplastic lymphangitis of the perigastric tissue; this is more amenable to total gastrectomy, even though such an operation is unlikely to be curative in nature.

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# Place of routine operative cholangiography at cholecystectomy

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Controversy exists about the exact indications for operative cholangiography at open cholecystectomy. Opinion is divided as to whether cholangiography should be performed in all cholecystectomies[1–5] or only in selected cases, as suggested in most recent publications[6–13]. A recent survey of practice among a group of general surgeons in the UK showed that 84 per cent performed operative cholangiography at all procedures and 12 per cent did so only in selected cases[14]. The novel technique of laparoscopic cholecystectomy has highlighted this debate; the place of cholangiography within or preceding this procedure is ill defined[15]. We believe that the same criteria for the need for cholangiography should be applied irrespective of the technique of cholecystectomy, and therefore that studies relating to open cholecystectomy can be used as guidelines to indications for cholangiography at the laparoscopic operation.

Cholangiography enables the surgeon to identify common duct stones and to define ductal anatomy. The controversy is whether cholangiography is necessary to achieve this in all cases. There is now strong evidence that a policy of selective cholangiography is justified for elective cholecystectomy.

## Detection of common bile duct stones

The overall incidence of common bile duct (CBD) stones has varied[8,16] between 7 and 30 per cent when routine cholangiography has accompanied open cholecystectomy. In recent series[2–4,6,8,10,13], however, the incidence has been about 10 per cent. A number of studies have examined the importance of operative cholangiography in the detection of unsuspected CBD calculi during open cholecystectomy and have suggested a variety of preoperative and intraoperative criteria that can exclude such stones without operative cholangiography[6–8,10–12]. Unfortunately, the criteria used have varied between series and all have evaluated intraoperative as well as preoperative criteria.

Preoperative criteria alone can identify patients with a low risk of common duct stones. There is general agreement that duct stones will be found in only 3–9 per cent of patients who have never been jaundiced[13,16–18]. Yip and Lam[13] found duct stones in only 3 per cent of those who had not been jaundiced, 7 per cent of patients with no history of pancreatitis and 5 per cent of those with no abnormality of plasma transaminase, alkaline phosphatase and bilirubin levels. Ijzermans *et al.*[10] found duct stones in 8 per cent of patients with no history of jaundice and in none of 215 with normal enzyme and bilirubin levels. Very few duct stones will be missed if operative cholangiography is omitted in patients with no history of jaundice or pancreatitis, and whose liver function test results and serum amylase estimations are normal.

Those who advocate cholangiography at all cholecystectomies may regard it as unacceptable if any duct stones are left undetected. Murison *et al.*, however, in a preliminary report[19], showed that cholangiography could be performed selectively with no risk of symptomatic stones remaining undetected. They performed selective cholangiography using criteria similar to those in *Table 1*. A further 285 patients who did not fulfil these criteria were randomized to operation with or without cholangiography. Stones were found in 12 per cent of these random cholangiograms and removed without complication. In contrast, no patient who did not undergo cholangiography developed symptomatic bile duct stones during at least 3 years of follow-up. Thus cholangiography may be selectively omitted in the safe knowledge that symptomatic bile duct stones will not present subsequently.

False-positive cholangiograms pose a different problem. False-positive rates (false positives per total number of cholangiograms) are low[1–4,6,8–13,16–18], ranging from 1·8 to 7 per cent. This, however, is to be expected when common duct stones are on average found in only 10 per cent of patients[2–4,6,8,10,13]. A better measure of the usefulness of operative cholangiography is its positive predictive value (PPV), given by the ratio of the number of cholangiograms truly positive for common duct stones to the number both truly and falsely positive. The PPV varies from 63 to 92 per cent in published studies[3,9]. In 15 series a total of 976 common duct explorations were undertaken on the basis of operative cholangiograms, and in 190 (19 per cent) no abnormality was found after exploration[1–4,6–13,16–18], a PPV of 80 per cent. There is some evidence that negative duct exploration is associated with a greater risk of complications than choledocholithotomy; it is difficult to explore and close small-calibre ducts safely[20]. Furthermore, a false-positive cholangiogram at laparoscopic cholecystectomy may unnecessarily commit the patient to an open operation or a second endoscopic procedure.

Other 'intraoperative' criteria (multiple small stones, CBD diameter) can be assessed before operation by ultrasonography, which can further increase the accuracy of prediction of those who are very unlikely to have duct stones. It is true that ultrasonography is relatively inaccurate in the detection of stones in the CBD[21]; it is less well appreciated that the finding of a CBD <3 mm in diameter effectively excludes a common duct stone[21]. In such patients there is nothing to be gained by operative cholangiography. Therefore, it is appropriate to perform cholangiography for the detection of duct stones selectively, using the criteria shown in *Table 1*. In this way unnecessary interventions based on false-positive cholangiographic findings will be minimized and few stones will be missed. After 453 laparoscopic cholecystectomies in which operative cholangiography was attempted on a selective basis, only two patients had symptoms suggestive of duct stones after operation[22].

The criteria in *Table 1* are accepted by many authors for the selection of patients for operative cholangiography at open cholecystectomy[6–11,13]. We use these criteria to select patients for preoperative endoscopic cholangiography before –

**Table 1** *Indications for cholangiography at or preceding cholecystectomy*

| | |
|---|---|
| History | Jaundice<br>Pancreatitis |
| Plasma biochemistry (elevated values) | Bilirubin<br>Amylase<br>Transaminases<br>Alkaline phosphatase |
| Ultrasonography | Common bile duct diameter >5 mm |

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laparoscopic cholecystectomy This enables duct stones to be detected before surgery, allows preoperative clearance of the duct, and avoids the difficulty of dealing with duct stones at laparoscopic cholecystectomy.

### Anatomy of extrahepatic bile ducts

A quite separate issue is the value of operative cholangiography in demonstrating the anatomy of the bile ducts, particularly as anomalies are common[23]. Duct injury may also be demonstrated by cholangiography. Approximately 0·5 per cent of patients undergoing conventional cholecystectomy sustain an extrahepatic bile duct injury[24,25]. Proponents of routine operative cholangiography, both at conventional[26] and laparoscopic[27] operations, claim that its use minimizes the chance of bile duct damage and allows immediate recognition and repair of some injuries. Series of patients who have sustained iatrogenic biliary strictures as a result of operative injury appear to contain relatively few who underwent operative cholangiography at the time of the original operation when compared with overall rates for operative cholangiography[14,26,28]. However, it has been demonstrated that operative cholangiography can be omitted or performed selectively with no apparent excess risk of bile duct injury in both open[19] and laparoscopic[21] cholecystectomy The detection of abnormal biliary anatomy was given as the principal reason for performing routine operative cholangiography in a recent large series of patients undergoing laparoscopic cholecystectomy, this policy did not, however, eliminate ductal injuries[27]. No ductal injuries occurred in a series of similar size in which selective cholangiography was used[22].

It must be acknowledged that there is a potential advantage to routine cholangiography. If the surgeon, radiographer and operating room team are all familiar with the technique then, in a case in which the procedure is necessary, it is more likely that high-quality radiographs will be obtained The regular performance of operative cholangiography develops expertise, reduces the time taken for the procedure and maintains the surgeon's skill in the interpretation of results.

### Evaluation of bile ducts before operation

Evaluation of the bile ducts before operation may avoid the need for routine operative cholangiography, particularly if the main purpose is to exclude bile duct stones. Clinical and ultrasonographic criteria can predict patients with a high risk of duct stones, as discussed above. Patients at low risk can then undergo operation without cholangiography, unless there are specific operative difficulties that require anatomical definition

Detection of patients at high risk for duct stones allows preoperative cholangiography and endoscopic management of any stones found Although there is no benefit from this technique before open cholecystectomy in young patients with duct stones[29] (compared with surgical duct exploration), the balance has probably shifted with the introduction of laparoscopic cholecystectomy. The difficulty of dealing with bile duct stones during this procedure confers considerable advantage on preoperative detection and treatment of such stones. Preoperative endoscopic cholangiography has been used in some series of laparoscopic cholecystectomies when jaundice or other factors have predicted a substantial risk of bile duct pathology[22,30]. Pancreatitis and other morbidity related to endoscopic cholangiography or sphincterotomy have not been a major problem.

High-dose intravenous cholangiography with modern contrast agents has been used to evaluate patients about to undergo laparoscopic cholecystectomy[31,32]. The accuracy of this technique appears to be little different from that of operative cholangiography performed during open cholecystectomy[33]. It may be useful for screening patients with clinical, biochemical or ultrasonographic criteria of risk to select for endoscopy those who will need endoscopic sphincterotomy and bile duct clearance before surgery. Intravenous cholangiography, however, finds little favour with surgeons and radiologists in the UK at present; cholangiography obtained by percutaneous puncture of the gallbladder may prove to be an attractive alternative. The latter approach produces cholangiograms of excellent quality, provides reliable information on the presence or absence of bile duct stones and gives a clear demonstration of ductal anatomy. However, it is invasive and its use should be limited to the immediate preoperative period.

### Operative cholangiography at laparoscopic cholecystectomy

The rapid surge in the popularity of laparoscopic cholecystectomy should not be allowed to obscure the fact that bile duct stones cause symptoms and morbidity. The difficulty of dealing with bile duct stones at laparoscopic cholecystectomy may tempt some surgeons to abandon cholangiography and hope that the ducts are clear. This temptation should be resisted: indications for cholangiography should be the same whatever the technique of cholecystectomy. The only difference that laparoscopic cholecystectomy introduces is the concept of preoperative endoscopic cholangiography and sphincterotomy in place of operative cholangiography and exploration of the CBD

A number of series have now shown that there is no great difficulty in obtaining operative cholangiograms in the course of laparoscopic cholecystectomy[22,27,34]. A median time of 20 min was required for cholangiography in one of these[34]. There is a 60–90 per cent success rate when cholangiography is attempted in all cases[22,27,34] and failure is often associated with a very narrow cystic duct which reduces the likelihood of passage of stones into the CBD[35]. A simplified technique has recently been described[36].

At present it is difficult to compare the results of selective and routine cholangiography at laparoscopic cholecystectomy because selection of patients for these procedures has differed between series. For example, preoperative infusion cholangiography showed no duct stones in one series of 36 patients[31], which suggests that a degree of selection had occurred even before intravenous cholangiography. As more series are reported (including operations on patients with acute presentations), it is becoming clear that most surgeons are selecting out patients with a high risk of bile duct stones. Such stones when found at laparoscopy are rarely cited as an indication for conversion to open operation. Either the surgeon has chosen to leave duct stones for later endoscopic extraction or he or she has been able to detect and deal with them before laparoscopic cholecystectomy. We believe that the latter is preferable as it avoids the dilemma posed by endoscopic failure after surgery, when additional invasive therapy may become necessary.

### Conclusions

The decision to obtain a cholangiogram should not be influenced by the method of cholecystectomy. Cholangiography should be performed selectively at both laparoscopic and open cholecystectomy on the basis of abnormal liver function test results, a history of pancreatitis or jaundice, or dilatation of the CBD demonstrated at operation or by preoperative ultrasonography. For patients undergoing open cholecystectomy, cholangiography is most conveniently obtained at operation. In contrast, selective preoperative cholangiography is appropriate before laparoscopic surgery. Intraoperative cholangiography should always be performed in the few patients in whom there is doubt about biliary ductal anatomy or when there is any suggestion of injury to the bile duct. The decision not to perform cholangiography should be made only according to defined criteria; its omission places a greater responsibility on the surgeon to define clearly the anatomy of the bile ducts

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# Isolated hyperthermic liver perfusion with cytostatic-containing perfusate activates the complement cascade

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*Eight patients with advanced liver malignancy undergoing isolated hyperthermic liver perfusion with melphalan and cisplatin were studied with regard to complement activation and formation of anaphylatoxins (C3a and C5a) and terminal C5b-9 complement complexes (TCCs). Blood samples for complement variables (C1-INH, C3, C4, C5, C3a, C5a and TCCs) were taken before surgery, 1 min before the start of perfusion, 1, 2 and 3 h after the start of perfusion, and 24 h after operation. Samples were drawn from the perfusate 1 h after the start of perfusion. Activation of complement was observed during perfusion. Raised plasma concentrations of C3a and TCCs were recorded and high levels of C3a and TCCs were found in the perfusate.* In vitro *tests indicated that melphalan and cisplatin may activate complement. This activation occurred at 37 and 42°C but was more pronounced at 42°C.*

Liver perfusion with cytostatic-containing perfusate for cancer therapy was introduced 30 years ago[1] and may induce regression of liver metastases from colorectal cancer[2]. Regional hyperthermia has been used for tumour therapy with positive results[1,3]. Procedures for isolation and hyperthermic perfusion of the liver have been described[4,5]. Pharmacokinetic studies of melphalan indicate that the spillover from the perfusate to the general circulation as measured by the melphalan concentration in systemic blood is minimal: the peak concentration of melphalan in the perfusate was 50–60 times higher than in the systemic circulation[6]. The perfusate is circulated by an extracorporeal procedure; during coronary bypass surgery such circulation activates the complement cascade[7,8]. When complement is activated biologically active anaphylatoxins (C3a and C5a) and terminal C5b-9 complement complexes (TCCs) are released[9,10]

C3a and C5a increase vascular permeability, contract smooth muscle and induce release of histamine from mast cells and basophils[11,12]. C3a causes cardiac dysfunction[13]; C5a is highly chemotactic for neutrophils, causing aggregation and stimulating oxidative metabolism[14,15]; TCCs stimulate macrophages and platelets, resulting in synthesis of prostaglandins and thromboxane[16,17]. Complement activation with the release of anaphylatoxins and TCCs is one mechanism behind the development of multisystem organ failure[18–21].

Complement can be activated in two ways: the classical pathway can be initiated by immune complexes and bacteria[22,23]; the alternative pathway can be activated by foreign materials or by tissue changes induced by heat, trauma or hypoperfusion[24–26]. Destruction of injured cells will lead to complement activation with release of biologically active split products from the cascade[27].

This study determined whether complement is activated by perfusion of the liver with cytostatic-containing hyperthermic perfusate and whether cytostatics (cisplatin and melphalan) and hyperthermia initiate activation of the complement cascade *in vitro*.

## Patients and methods

### *Clinical studies*

Eight patients of mean age 47 (range 37–59) years with irresectable secondary liver cancer were studied Four had primary malignant melanoma and the others had primary tumours of the intestine (two patients), kidney (one) and ovary (one). Age, sex, weight, diagnosis and postoperative complications are shown in *Table 1*.

### *Technique*

All patients underwent liver perfusion with hyperthermic and cytostatic-containing perfusate, mean temperature 41·6 (range 41·1–42·1)°C under general anaesthesia The cytostatic agents used were cisplatin and melphalan; the perfusion procedure is illustrated schematically in *Figure 1*. The liver was isolated from the systemic circulation with a double-lumen catheter (Perfufix, Braun, Melsungen, Germany) inserted in the inferior vena cava, and by ligation of the portal vein and hepatic artery. Venous blood flow from the lower part of the body was transferred through the inner lumen of the catheter to the heart without being mixed with hepatic venous blood. Intestinal blood flow bypassed the liver from the portal vein through a shunt to the inner lumen of the catheter. The extracorporeal circulation was established by connecting the outer lumen of the catheter to a pump-oxygenator (Gambro roller pump; Lund, Sweden and Dideco Master Flow 701; Mirandola, Italy) and a heat exchanger (Dideco Master Flow 701) and recirculated to the portal vein and hepatic artery. When the temperature in the liver parenchyma had reached 40·0°C, melphalan (0·5 mg per kg body-weight) was added to the perfusion circuit Perfusion was continued for 60 min after the administration of melphalan. Cisplatin was added in increasing doses (0 1–0·7 mg per kg body-weight) to the perfusate as a bolus injection 40 min after perfusion with melphalan Arterial and central venous pressures were monitored continuously.

**Table 1** *Details of eight patients undergoing liver perfusion*

| Patient no | Age (years) | Sex | Weight (kg) | Diagnosis | Complications |
|---|---|---|---|---|---|
| 1 | 59 | F | 75 | Melanoma | MSOF |
| 2 | 51 | M | 82 | Renal cancer | — |
| 3 | 37 | M | 91 | Melanoma | — |
| 4 | 43 | F | 82 | Ovarian cancer | — |
| 5 | 40 | F | 66 | Melanoma | MSOF |
| 6 | 59 | F | 53 | Colonic cancer | — |
| 7 | 40 | M | 92 | Carcinoid | — |
| 8 | 38 | M | 72 | Melanoma | — |

MSOF, multisystem organ failure

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Levels of the complement variables C1-INH, C3, C4, C5, C3a, C5a and TCC were determined before surgery, 1 min before the start of perfusion, 1, 2 and 3 h after the start of perfusion, and 24 h after operation Blood samples were drawn from the radial artery. Concentrations of the complement variables in the perfusate were measured 1 h after the start of perfusion.

All samples for complement determinations were drawn into tubes with ethylenediamine tetra-acetic acid (EDTA) to prepare plasma. 0·054 ml 0·34 mol/l EDTA per 4·5 ml blood. The tubes were centrifuged at room temperature (20–22°C) to remove the cells and the samples frozen within 30 min and stored at −80°C until levels of the complement variables were determined. All assays were performed in duplicate and all samples were analysed immediately after thawing; none was refrozen. The samples were stored in different tubes for different analyses.

Levels of serum bilirubin, aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT) and creatinine as well as the platelet count were measured regularly during and after perfusion.

### *Complement analysis*

The complement components C1-INH, C3, C4 and C5 were assayed by rocket immunoelectrophoresis[28]. The plasma concentrations of C3a and C5a antigens were determined with a radioimmunoassay method[29,30]. TCC was analysed by a double-antibody enzyme-linked immunosorbent assay method[31].

### In vitro *methods*

Melphalan and cisplatin were incubated in fresh human serum and in heparinized whole blood from six healthy individuals at 37 and 42°C for 15 min and at concentrations of 0·01 and 0·1 mg per ml serum or heparinized whole blood. EDTA was added to the serum after 15 min incubation; the cells in the heparinized whole blood samples were removed by centrifugation, and EDTA then added. All tubes were kept at −80°C until the concentrations of C1-INH, C3, C4, C5, C3a, C5a and TCC were determined. All assays were performed in duplicate

### *Statistics*

Median (range) values were calculated The Wilcoxon rank sum test was used for statistical analysis of differences between groups. The Wilcoxon test for paired comparisons was used for statistical analysis within groups. Differences were considered significant at $P < 0·05$

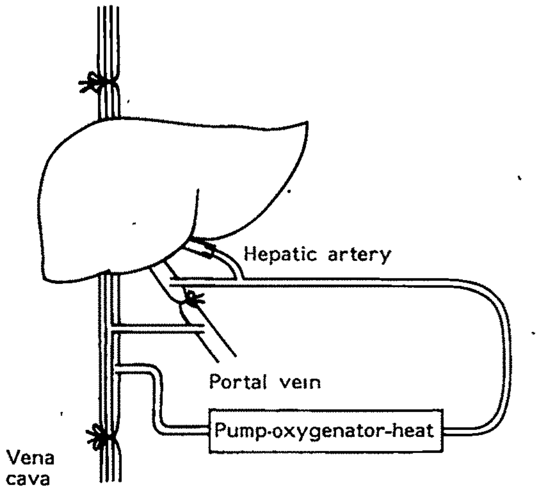

**Figure 1** *Schematic illustration of the liver perfusion procedure*

**Table 2** *Haematological variables of eight patients*

| | Reference level | Preoperative level* | Postoperative level* |
|---|---|---|---|
| Bilirubin (μmol/l) | 3·4–21 | 13·8(4·9) | 174(99) |
| ASAT (μkat/l) | <0·7 | 1·1(0·4) | 47(22) |
| ALAT (μkat/l) | <0·7 | 0·6(0·1) | 25(11) |
| Creatinine (μmol/l) | 50–150 | 90(9) | 206(58) |
| Platelet count (×10⁹ cells/l) | 150–400 | 87(6) | 36(4) |

*Values are mean(s.e.m.). ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase

## Results

### *Perfusion studies*

Two patients developed multisystem organ failure with pulmonary, renal and hepatic insufficiency and died after 7 and 23 days. Both had extensive liver metastases from malignant melanoma. Preoperative and postoperative levels of serum bilirubin, ASAT, ALAT and creatinine and the platelet count are shown in *Table 2.*

Levels of complement variables C1-INH, C3, C4, C5, C3a, C5a and TCCs are shown in *Table 3.*

During the perfusion procedure C1-INH, C3, C4 and C5 decreased· 1 h after the start of perfusion, all were significantly lower than before perfusion began. There were no significant differences between patients who later developed multisystem organ failure and those with no signs of organ dysfunction after surgery.

During perfusion, C3a concentration increased compared with the preoperative levels and those 1 min before perfusion ($P < 0·001$).

The plasma concentrations of TCCs increased at 1, 2 and 3 h after the start of perfusion compared with the preoperative levels and 1 min before perfusion.

The concentrations of C3a and TCCs in the perfusate were all significantly ($P < 0·001$) increased relative to the levels in systemic blood at the same time. The C5a level in the perfusate was <10 ng/ml in all samples. There were no significant differences in C1-INH, C3, C4 and C5 levels between the perfusate and the systemic blood.

### In vitro *studies*

The results of incubation with melphalan or cisplatin in fresh human serum and in heparinized whole blood are shown in *Table 4.*

Incubation of serum for 15 min at 42°C gave higher C5a and TCC concentrations than at 37°C, but the differences

**Table 3** *Complement variables for eight patients studied*

| Variable | Preoperative level | Level 1 min before perfusion | Level after start of perfusion 1 h | 2 h | 3 h | Level 24 h after surgery | Level in perfusate |
|---|---|---|---|---|---|---|---|
| C1-INH (μg/ml) | 30·5 (17·6–77·7) | 21 (13·7–31·9) | 14·7 (13·7–31·5) | 16·6 (9·0–23·1) | 18·3 (10·5–31·5) | 23·1 (16·8–29) | 15·1 (9·7–31·5) |
| C3 (mg/ml) | 3·8 (1·8–5·1) | 3·7 (1·0–5·1) | 2·4 (1·0–3·5) | 1·8 (0·7–4·8) | 2·6 (2·3–3·9) | 2·8 (2·3–3·4) | 2·0 (0·7–5·1) |
| C4 (μg/ml) | 745 (588–1446) | 678 (298–813) | 542 (271–902) | 452 (325–696) | 452 (298–904) | 329 (208–452) | 452 (271–904) |
| C5 (μg/ml) | 324 (240–480) | 190 (93–396) | 120 (60–240) | 120 (94–300) | 150 (108–300) | 222 (84–360) | 180 (60–480) |
| C3a (ng/ml) | 408 (216–748) | 596 (380–844) | 752 (353–1548) | 1008 (336–2196) | 1448 (524–1940) | 816 (320–1056) | 1348 (988–3684) |
| C5a (ng/ml) | 4 (4–5) | 4 (4–7) | 4 (4–6) | 4 (4–4) | 4 (4–8) | 4 (4–4) | 5 (4–7) |
| TCCs (units/ml) | 2 (1–4) | 2·5 (1–7) | 3 (2–17) | 4 (2–22) | 5·5 (3–13) | 3 (2–7) | 6 (2–25) |

Values are median (range) TCCs, terminal C5b-9 complement complexes

**Table 4** *Complement variables after incubation of serum with melphalan or cisplatin for 15 min*

| | Control | Melphalan | | Cisplatin | |
|---|---|---|---|---|---|
| | | 0·01 mg/ml | 0·1 mg/ml | 0·01 mg/ml | 0·1 mg/ml |
| C3a (μg/ml) | | | | | |
| Serum | | | | | |
| 37°C | 2·6(0·3) | 2·6(1·0) | 3·8(0·6) | 2·8(0·4) | 3·4(0·6) |
| 42°C | 3·7(0·4) | 3·8(0·4) | >4 | 3·7(0·5) | >4 |
| Blood | | | | | |
| 37°C | 0·3(0·1) | 0·3(0·2) | 1·9(0·5) | 0·3(0·1) | 0·3(0·1) |
| 42°C | 0·6(0·2) | 0·5(0·2) | 2·2(0·7) | 0·5(0·3) | 0·5(0·1) |
| C5a (ng/ml) | | | | | |
| Serum | | | | | |
| 37°C | <10 | <10 | <10 | <10 | <10 |
| 42°C | 13(3) | <10 | <10 | 13(3) | 16(4) |
| Blood | | | | | |
| 37°C | <10 | <10 | <10 | <10 | <10 |
| 42°C | <10 | <10 | <10 | <10 | <10 |
| TCCs (units/ml) | | | | | |
| Serum | | | | | |
| 37°C | 2·3(0·7) | 3·3(1·9) | 2·3(0·3) | 2·9(1·2) | 4·2(2·7) |
| 42°C | 5·1(3·0) | 3·1(0·9) | 4·0(1·6) | 5·1(3·0) | 8·4(5·6) |
| Blood | | | | | |
| 37°C | 1·1(0·1) | 3·3(1·9) | 1·8(0·5) | 1·1(0·2) | 1·9(0·9) |
| 42°C | 1·9(0·6) | 1·1(0·2) | 1·7(0·4) | 1·9(0·6) | 2·7(1·4) |

Values are mean(s.e.m.). TCCs, terminal C5b-9 complement complexes

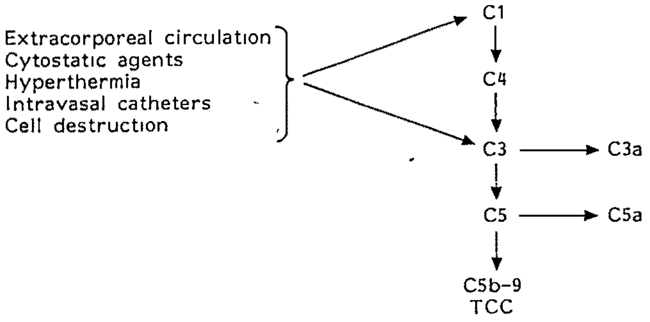

**Figure 2** *Schematic and simplified illustration of the complement cascade. TCC, terminal complement complex*

regarding the C3a concentrations were not significant. Incubation of heparinized whole blood increased formation of C3a and TCCs at 42°C compared with 37°C; no significant differences were found in the concentrations of C5a.

When the experiments were performed in the presence of melphalan (0·01 or 0·1 mg/ml), no significant differences were observed at the two temperatures. In contrast, when cisplatin (0·01 or 0·1 mg/ml) was present in serum the formation of C5a and TCCs was higher at 42 than at 37°C. No such differences were found for C3a, but the C3a concentrations were higher when melphalan (0·01 mg/ml) or cisplatin (0·01 or 0·1 mg/ml) was incubated in heparinized whole blood. Incubation of heparinized whole blood with 0·1 mg/ml melphalan increased formation of C3a; no significant differences were observed when melphalan was incubated in serum. Similarly, no significant differences in C5a or TCC production were seen when melphalan was incubated in heparinized whole blood. Incubation of serum and heparinized whole blood with cisplatin (0·01 or 0·1 mg/ml) resulted in significant ($P < 0·05$) formation of TCCs, but no significant changes in C3a and C5a levels occurred after incubation with cisplatin.

## Discussion

The complement cascade is activated when isolated hyperthermic liver perfusion with cytostatic-containing perfusate is performed on patients with liver malignancy, as evidenced by the formation of anaphylatoxins and TCCs in systemic blood and in the perfusion circuit. In addition, decreased levels of the complement products C1-INH, C3, C4 and C5 indicate a consumption of complement proteins.

Several studies have found a relationship between the degree of complement activation and the development of adult respiratory distress syndrome and multisystem organ failure in the critically ill[18–21]. Langlois and Gawryl have demonstrated that high plasma TCC levels may be an early indicator of adult respiratory distress syndrome in patients with sepsis[21]. In those undergoing aortic surgery, raised C3a concentrations have been demonstrated before the onset of complications such as pulmonary, hepatic and renal dysfunction[32].

In the present study, two of eight patients developed multisystem organ failure after liver perfusion. There are several possible causes of initiation of the complement cascade with such perfusion (*Figure 2*). *In vitro* studies indicate that melphalan and cisplatin activate the complement cascade, with or without cells present, and that it is not the injured cells that stimulate anaphylatoxin and TCCs. However, melphalan and cisplatin do not seem to be very potent activators of the complement cascade; bacteria such as *Escherichia coli*, even in small concentrations, release much higher amounts of anaphylatoxins and TCCs[33]. The high temperature of the perfusate may stimulate the reactivity of complement. The present studies indicate that the formation of split products is higher at 42°C than at 37°C and control experiments demonstrate that the spontaneous formation of C3a and TCCs is more pronounced at 42°C than at 37°C. The increased formation of C5a and TCCs after incubation in heparinized whole blood compared with serum may be explained by effects of the cytostatic agent on the cells rather than a primary effect on the complement cascade. A primary complement-activating effect might allow formation of C5a and TCCs in serum without the presence of cells. Injured cells will activate complement, with the release of anaphylatoxins[27].

Extracorporeal circulation seems to be the most important individual factor leading to complement activation during liver perfusion. In coronary bypass surgery extracorporeal circulation results in formation of anaphylatoxins and TCCs; the plasma levels of circulating C3a and TCCs found during liver perfusion are lower than those found during coronary bypass surgery[7,8,33]. Foreign materials such as synthetic graft materials used in vascular surgery activate the alternative pathway of complement[25]. The Perfufix catheter used to bypass the liver is in direct contact with circulating systemic blood during perfusion and may lead to anaphylatoxin and TCC formation. The presence of high TCC concentrations in systemic blood during liver perfusion demonstrates that the terminal part of the complement cascade is activated. The lack of raised C5a concentrations is probably the result of differences in elimination of the anaphylatoxins: since C5a and its inactivated form bind to leucocytes, it is impossible to detect an increase in C5a until the neutrophil-binding capacity is exceeded.

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# Biodistribution of Lipiodol following hepatic arterial injection

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*Thirteen patients undergoing selective coeliac angiography before insertion of an indwelling hepatic arterial cannula underwent injection of 3 ml radiolabelled Lipiodol (2 MBq $^{131}$I) into the hepatic artery at the end of the procedure. At subsequent laparotomy 1–9 days later, biopsies were taken from normal liver and metastases. The radioactivity of this material was measured to establish the tumour:liver ratios. Two patients with large metastases ($>$10 cm in diameter) had low ratios. In the remainder, the median ratio at 24 h was 1·5:1 (range 1·1–2·5:1;* n = 5*) and 2·6:1 (range 1·5–64·0:1;* n = 6*) at 3–9 days. Four patients underwent single photon emission computed tomography, which confirmed selective retention of Lipiodol in small metastases, although no activity was detected in a large deposit ($>$15 cm) 10 days after injection. The tumour:liver ratio in the other three patients increased from 3·0–5·6:1 on day 1 to 4·5–7·2:1 on day 6. This study suggests that Lipiodol may be a useful therapeutic delivery agent to small colorectal liver metastases.*

Lipiodol (May and Baker, Dagenham, UK) is an iodinated ester derived from poppy-seed oil that has been used as a radiographic contrast agent for many years and is selectively retained within hepatic tumours[1]. Utilizing this effect, it can be combined with either anticancer drugs or radioiodine ($^{131}$I) in the treatment of primary hepatomas[2–4]. The possibility of treating secondary liver tumours in a similar fashion has been proposed[4], but the results are inconclusive and little attempt has been made to obtain accurate dosimetry in metastases, although this has been done in hepatocellular carcinoma[5].

The aim of this study was to assess the biodistribution of radiolabelled Lipiodol following hepatic arterial injection in patients with colorectal liver metastases, to achieve accurate dosimetry.

## Patients and methods

Thirteen patients with colorectal liver metastases referred for treatment by resection or long-term hepatic arterial chemotherapy were studied. All underwent selective angiography to assess hepatic arterial anatomy. At the end of the procedure the catheter was advanced into the common hepatic artery or one of its branches. A volume of 3 ml Lipiodol labelled with 2 MBq $^{131}$I was slowly infused under fluoroscopy and the catheter then flushed with saline At subsequent laparotomy, for resection or insertion of an arterial infusion catheter (1–9 days later), a biopsy was taken from a metastasis and from normal liver. The samples were weighed and the activity counted using a Gammamatic 1 automated counter (Kontron, St Albans, UK) set to a $^{131}$I window. The activity per gram of tissue was evaluated and the tumour.liver ratio calculated.

A further four patients received a hepatic arterial injection of 3–5 ml Lipiodol labelled with 40 MBq $^{131}$I These patients subsequently underwent serial single photon emission computed tomography (SPECT) using an IGE Maxi camera (IGE Medical Systems, Slough, UK). This allows areas of relatively increased activity to be compared with conventional computed tomography (CT) images. In addition, planar images of the abdomen, thorax and neck were acquired as well as whole-body profiles using a shadow shield whole-body counter (J&P Engineering, Reading, UK) to assess biodistribution Imaging was performed on all subjects on at least two occasions

The CT and SPECT images of each patient were transferred to a common image processing computer (VAX 11-730; Digital Equipment, London, UK, with Sigmex A7000 display processor; Sigmex, Horsham, UK) running the portable imaging computer software developed in this unit The two sets of images were aligned and the CT images used to correct the SPECT images for attenuation of radiation, allowing them to be calibrated in absolute activity per unit volume The whole liver volume was outlined and the corresponding activity calculated Areas of tumour in the liver were outlined on the CT image and the corresponding activity per unit volume assessed from the SPECT images. For each patient the tumour:liver dose ratio was calculated. Activity in the lung was assessed using quantitative analysis of planar scintigraphy, and the corresponding dose calculated

The whole-body counting data were used to assess the whole-body clearance curve for each subject, with data calibrated to injected activity at day 0 Subtraction of the liver and lung activities from the total activity in the patient enabled a calculation of total body activity, and hence total body dose could be obtained

## Results

### *Biopsy data*

Two patients underwent hemihepatectomy for a solitary metastasis, 8 cm in diameter in each. *Table 1* shows the data from multiple samples in these patients. Activity was low in the central part of the tumour and greater at the macroscopic tumour edge. Comparison of samples taken from the edge of the tumour with those from normal liver showed tumour:liver ratios of 1·5:1 and 2·2:1 on days 1 and 5 respectively after injection of Lipiodol.

In addition to two hepatectomies, 11 patients were assessed by biopsy. Altogether, six patients underwent laparotomy 24 h after Lipiodol injection Tumour:liver ratios of activity in these patients ranged from 0·5 to 2·5:1 (median 1·2:1) The remaining seven patients underwent laparotomy between 3 and 9 days after Lipiodol injection, and showed tumour.liver ratios of 0·2–64·0:1 (median 2·5:1).

### *Single photon emission computed tomography*

Three of the four patients underwent SPECT, performed on days 1 and 6 after Lipiodol injection. *Table 2* shows that between 80 and 90 per cent of the initial injected activity was retained within the liver. The remaining activity was located over the lungs. *Figure 1* shows a SPECT image taken on day 6 overlaid on a corresponding CT image 7 days after Lipiodol angiography. The activities derived from areas of tumour and non-tumour were used to derive the tumour:liver ratios (*Table 2*). The fourth patient who underwent SPECT, on days 6 and 10 after Lipiodol injection, had a large deposit (approximately 15 cm) which failed to show any activity. A

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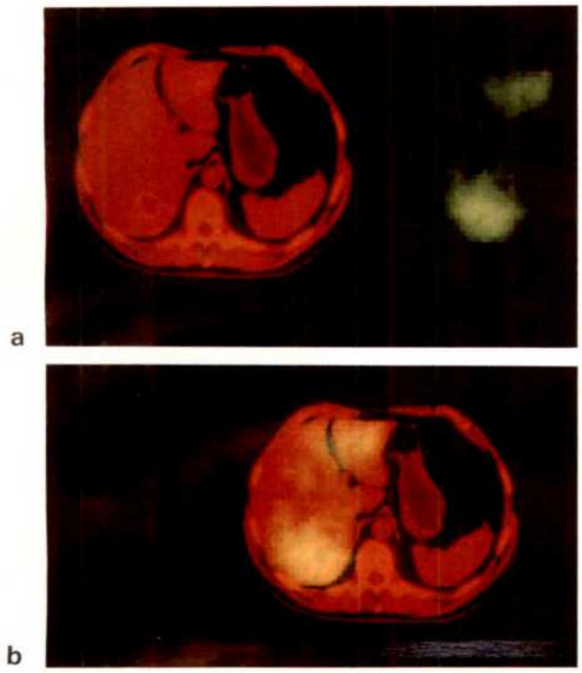

**Figure 1** **a** *Single photon emission computed tomography (SPECT) image (right) and corresponding computed tomography (CT) image (left). Liver metastases seen on the conventional CT scan are enhanced by Lipiodol deposition; green areas are those of increased activity on a corresponding SPECT image.* **b** *Computer overlay of the two images demonstrates that the areas of increased activity correspond to metastases*

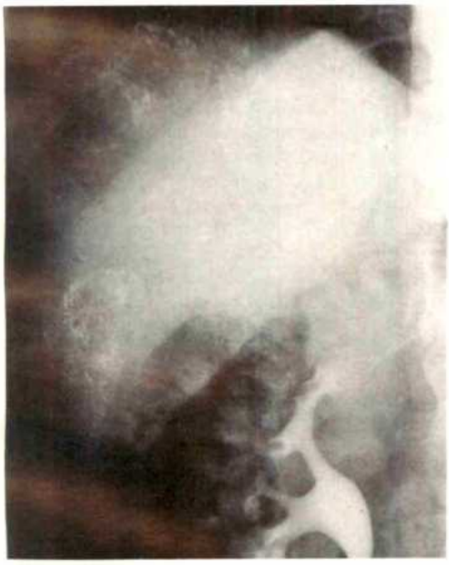

**Figure 2** *Abdominal radiograph immediately after hepatic arterial injection of Lipiodol showing preferential deposition at the periphery of metastases*

**Table 1** *Activity of liver tissue and tumour in two patients who underwent hemihepatectomy*

| | Radioactivity (c.p.m. per g tissue) | |
|---|---|---|
| | Patient 1 (at 24 h) | Patient 2 (at 5 days) |
| Tumour | | |
| Centre | 32 145 | 5 800 |
| Edge | 117 702 | 23 880 |
| Normal liver | 80 671 | 10 690 |
| Tumour:liver ratio* | 1·5:1 | 2·2:1 |

*Compares activity in samples from tumour edge and normal liver

**Table 2** *Tumour:liver activity ratios derived from single photon emission computed tomography*

| Patient no. | Amount of injectate in liver (%) | Tumour:liver ratio | |
|---|---|---|---|
| | | At 24 h | At 6 days |
| 1 | 90 | 3·0:1 | 4·5:1 |
| 2 | 80 | 4·7:1 | 6·0:1 |
| 3 | 88 | 5·6:1 | 7·2:1 |
| 4 | 76 | | 2·0:1 |

second small metastasis had a tumour:liver ratio of 2·0:1, which remained unchanged over the study period.

No activity was detected over the thyroid gland in any of these patients.

*Conventional imaging*

The peripheral distribution of Lipiodol in colorectal liver metastases after intra-arterial injection was confirmed by plain radiography (*Figure 2*) and CT (*Figure 3*).

## Discussion

Despite much effort, results of treatment of established multiple colorectal liver metastases remain depressing. The chemotherapeutic agent that has shown most benefit is 5-fluorouracil. When this is given through a hepatic arterial cannula[6], some patients obtain a survival benefit[7]. Lipiodol has been widely employed in the treatment of irresectable primary hepatoma with some effect[2,4] since Nakakuma *et al.*[1] demonstrated that it is selectively retained by these tumours. There have been attempts to treat liver metastases in a similar fashion, but only a slight benefit has been shown in small studies[4,8,9]. This may be because the agents employed have little effect against colorectal metastases or, in the case of radioiodine, because an ineffective dose may have been used.

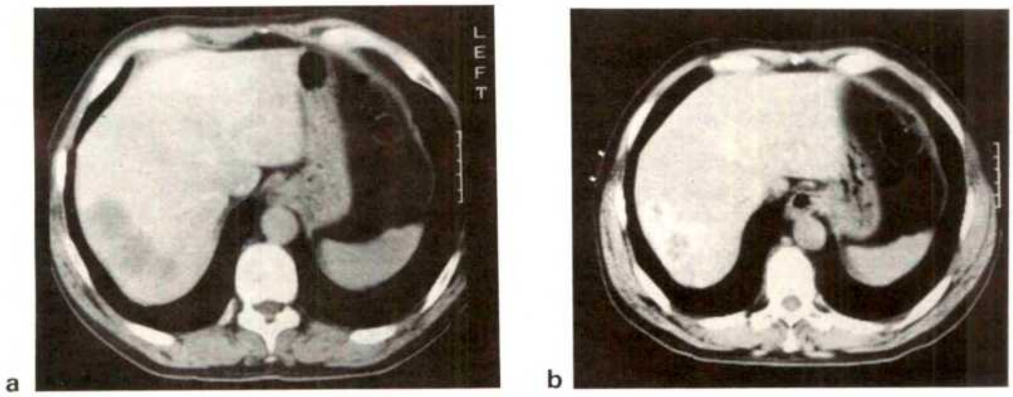

**Figure 3** **a** *Conventional computed tomography (CT) scan compared with* **b** *CT scan 7 days after Lipiodol injection. Lipiodol can be seen to be preferentially retained around the edge of the metastasis*

The aim of the present study was to demonstrate a method of accurately assessing individual dosimetry of patients with colorectal liver metastases by studying the biodistribution of Lipiodol after hepatic arterial injection. In two of the 13 patients in the biopsy study, activity within the central portion of a metastasis was low, whereas at the macroscopic edge activity was relatively high. Furthermore, the ratio of activity between tumour edge and normal liver increased with time, indicating that Lipiodol was retained longer in the tumour. Two biopsy samples taken from large metastases ($>10$ cm) showed a tumour:liver ratio of $<1$, whereas all other biopsies were taken from smaller tumours. Indeed, two biopsies taken from small metastases ($<5$ cm) gave tumour:liver ratios of 63·0:1 and 64·0:1. This may indicate that Lipiodol therapy is not suitable for all patients, and that its greatest potential is in the treatment of small multiple metastases. Further evaluation is needed to assess the optimal size for treatment. This would, however, be in keeping with the changing blood supply seen with increasing growth of liver metastases[10].

The four patients who underwent SPECT provided a sequential view of the tumour:liver activity for whole tumours in the same patient, thus eliminating any sampling error that may occur with biopsy data. A high tumour:liver ratio (3·0–5·6:1) was demonstrated at 24 h in three patients with multiple colorectal liver metastases, and this increased in each patient, to give values of 4·5–7·2:1 at 6 days.

Although these figures are remarkably high, and very encouraging, the actual activity at the tumour edge may well be much greater. The resolution of the $\gamma$ camera does not allow the expected central low activity to be separated from the area of higher activity at the periphery of the tumour. This is particularly the case for the high-energy $\gamma$ emissions of $^{131}$I, and at the relatively large distance between source and camera used in SPECT with circular orbit. These factors would have the effect of underestimating the tumour:liver ratios. It is apparent on plain radiographs taken immediately after Lipiodol infusion (*Figure 2*) that there is preferential deposition at the periphery of the tumour, and CT scans taken 7 days after Lipiodol injection show heavy deposition of Lipiodol concentrated at the tumour margin (*Figure 3*). One patient, although demonstrating increased activity in a small metastasis, had a very large tumour (approximately 15 cm in diameter) in the right lobe of the liver which failed to show any significant activity, presumably because of low vascularity of this large lesion.

More than 75 per cent of initial injected activity is retained in the liver (*Table 2*) and activity within the lungs remains less than that seen in the normal liver. No activity was detected over the thyroid, which suggests that no free iodine is present after injection of Lipiodol.

These initial results indicate that Lipiodol could prove to be a successful carrier agent for targeted internal radiotherapy in the treatment of liver metastases. Although uptake is variable, most patients, particularly those with multiple small deposits of tumour, show encouraging tumour:liver ratios of activity.

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# Fat-wrapping in Crohn's disease: pathological basis and relevance to surgical practice

*The connective tissue changes that accompany intestinal Crohn's disease have received little attention from pathologists. This is particularly so with fat hypertrophy, and yet surgeons have long recognized the phenomenon of fat-wrapping in the intestines and used it to delineate the extent of active disease. A consecutive, unselected series of 27 intestinal resections performed on 25 patients for histologically confirmed Crohn's disease was studied to correlate fat-wrapping with other clinicopathological features. Fat-wrapping was identified in 12 of 16 ileal resections and in seven of 11 large bowel resections. It correlated closely with transmural inflammation and there was a relationship between fat-wrapping and other connective tissue changes including fibrosis, muscularization and stricture formation. Morphometry demonstrated that there was true hypertrophy and that fat-wrapping does not relate solely to bowel wall shrinkage. There was correlation with ulceration but in 11 cases macroscopic ulceration extended beyond the fat-wrapping and in six to surgical resection margins. The pathological features of 225 small intestinal resections were reviewed and fat-wrapping was seen only in Crohn's disease. Fat-wrapping correlates best with transmural inflammation and represents part of the connective tissue changes that accompany intestinal Crohn's disease. Findings also suggest that fat-wrapping alone should not be used as an accurate marker of disease extent at the time of surgery.*

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The pathological diagnosis of Crohn's disease is established by a combination of macroscopic and microscopic features. Both are in turn related to a series of characteristic inflammatory changes and to less well recognized connective tissue changes. The latter include fibrosis, muscularization, neuronal hyperplasia and vascular alterations. Fibrosis is seen in both the submucosa and subserosa[1]. Muscularization in the submucosa is the result of proliferation of smooth muscle from the muscularis mucosa and also within a fibrotic submucosa[2]. Neuronal hyperplasia is characterized by an increase in the number of ganglion cells[3] and enlargement of nerve trunks[4]. Changes in the intestinal vasculature include degenerative arterial lesions and venous hyperplasia[5]. The final connective tissue change, fat hypertrophy or fat-wrapping, has long been recognized by surgeons but has been entirely neglected by pathologists. This study attempts to redress the lack of pathological interest in a phenomenon that appears to be a prevalent accompaniment to intestinal Crohn's disease.

## Patients and methods

A consecutive, unselected series of 27 resections performed on 25 patients for intestinal Crohn's disease at one institution (Gloucestershire Royal Hospital) was studied. Clinical data were recorded for each patient and the diagnosis of Crohn's disease established by histopathological assessment of the resected specimen and previous biopsies in conjunction with available clinical and radiological data. There were 16 resections for small bowel disease, including 11 right hemicolectomies with ileal disease only, three resections of ileocolic anastomoses with recurrent disease proximal to the anastomosis, and two specimens of ileal disease only. The 11 resections for large bowel disease included two right hemicolectomies with colonic disease only, eight segmental colonic resections and one proctectomy specimen. One resection was performed in 23 patients and two patients underwent two resections.

Because no clear definition of fat-wrapping exists, it was considered to be present when >50 per cent of the intestinal circumference was covered by adipose tissue in association with loss of the bowel–mesentery angle. This corresponds to descriptions in the surgical literature[6].

### *Histopathological preparation and assessment*

Each resection specimen was received unopened, in formalin. The bowel was washed out, both resection margins were clamped and the lumen was injected with 10 per cent buffered formalin. Adequate volumes of fixative were injected at 10-cm intervals until resistance was felt. After 24-h fixation, a full-size drawing was made on which areas of fat-wrapping, ulceration and stricturing were depicted. The length and circumferential extent of fat-wrapping were noted; macroscopic assessment of the other features of Crohn's disease was also undertaken at this time. In specimens with normal as well as fat-wrapped areas, large transverse whole-mount blocks were taken from both areas before opening the bowel. Each resection specimen was extensively sampled for histological examination to ensure a representative assessment of the pathological changes present. Tissues were routinely processed through paraffin wax and 4-$\mu$m sections stained with haematoxylin and eosin.

### *Histomorphometry*

Morphological parameters were measured on the large whole-mount slides of transverse sections of both normal and fat-wrapped intestine. External and internal diameters of the bowel, and the thickness of the mesentery, bowel wall and muscularis were analysed for each resection specimen using a Kontron MOP-Videoplan Image Analyser (Kontron Elektronik, Eching, Germany). Parameters for normal and fat-wrapped intestines were compared using Student's $t$ test.

### *Histopathological review*

To test the specificity of the finding of fat-wrapping for Crohn's disease, a histopathological review of 225 small intestinal resections performed over 5 years at Gloucestershire Royal Hospital was carried out. In each specimen the pathological features were assessed, including connective tissue changes, and the presence or absence of fat-wrapping determined by analysis of the serosal and subserosal tissues.

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## Results

Clinical data are shown in *Table 1* and pathological findings in *Table 2*. Nineteen resection specimens, 12 from the small bowel and seven from the colon, showed evidence of fat-wrapping as defined. There was no correlation between the presence or extent of fat-wrapping and age, sex, weight, smoking habit, duration of disease, extent of disease, or treatment. In general, fat-wrapping was easier to detect in small bowel resections (*Figures 1* and *2*) than in colorectal specimens. This was predominantly related to difficulty in assessing the extent of fat encroachment in the colon because the taeniae coli restrict fat encroachment and because of the prevalence of excess fat in the region of the appendices epiploicae. Nevertheless, in seven of the 11 colonic resections, fat-wrapping was clearly identified (*Figure 3*). Eighteen resection specimens showed ulceration in fat-wrapped areas, but in 11 macroscopic ulceration extended beyond fat-wrapped areas (range 2–51 cm) and in six resection specimens the ulceration, but not the fat-wrapped areas, extended to the surgical resection margins. In those areas with surface ulceration but without fat-wrapping, there was a notable absence of transmural inflammation. Pathological analysis thus showed fat-wrapping to correlate with ulceration and stricture formation, but the strongest association of fat-wrapping was with transmural inflammation (*Figure 4*). No differences were identified in the distribution of fat-wrapping and the other pathological parameters between small and large intestinal resection specimens.

Eight resection specimens did not show any evidence of fat-wrapping. Five of these were inflammatory masses in which the presence of external inflammation and adhesions due to fistulae and previous surgery made assessment of the external surface of the bowel impossible. Of the remaining three cases without demonstrable fat-wrapping, one resection specimen consisted of rectum and anus only, in which anatomy and

**Table 1** *Clinical data*

| | |
|---|---|
| Mean age (years) | 36·6 (14–80) |
| Sex ratio (M:F) | 15:10 |
| Mean weight (kg) | 57·6 (39–78) |
| Smokers:non-smokers | 15:10 |
| Mean duration of disease (years) | 7·3 (0·2–33) |
| Site of disease* | |
| Ileum | 16 |
| Colorectum | 10 |
| Anus | 1 |
| Mean extent of disease (cm) | 39·8 (12–85) |
| Treatment | |
| Systemic corticosteroids | 16 |
| Azathioprine | 1 |
| Sulphasalazine | 1 |
| Elemental diet | 20 |

Values in parentheses are ranges. *Total of 27 resections in 25 patients

**Table 2** *Correlation of pathological features with fat-wrapping*

| | Small bowel ($n = 16$) | Large bowel ($n = 11$) |
|---|---|---|
| Fat-wrapping | 12 | 7 |
| Correlated pathology | | |
| Mucosal ulceration | 12 | 6 |
| Transmural inflammation* | 11 | 6 |
| Granulomas | 8 | 3 |
| Strictures | 10 | 3 |
| Fibrosis | 12 | 7 |
| Muscularization | 11 | 5 |
| Neuronal hyperplasia | 12 | 7 |

*Only transmural inflammation correlated directly with fat-wrapping (other changes were also seen in non-fat-wrapped areas)

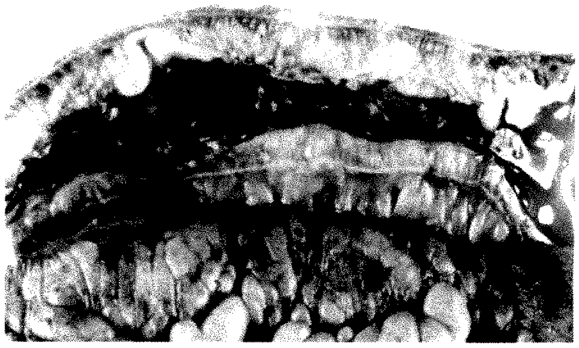

**Figure 1** *Fat-wrapping of the terminal ileum. The ileum shows the characteristic macroscopic features of Crohn's disease including stricturing, bowel wall thickening and focal mucosal ulceration. Corresponding to this there is fat encroachment on the antimesenteric surface of the ileum* (Figure 2)

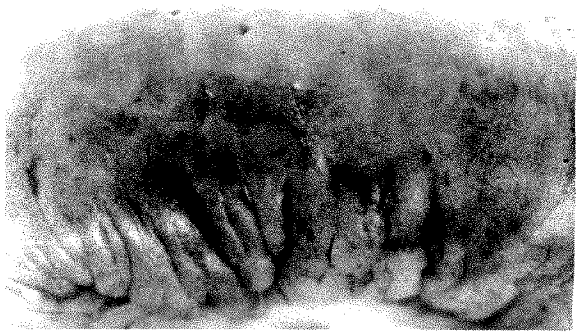

**Figure 2** *Fat encroachment completely enveloping the antimesenteric aspect of the ileum*

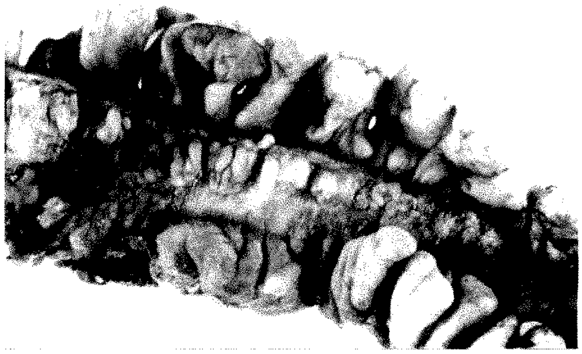

**Figure 3** *Fat-wrapping in the colon. Fat encroachment is clearly demonstrable between the antimesenteric taeniae*

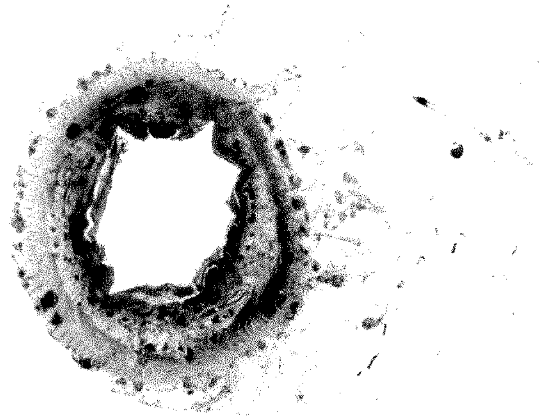

**Figure 4** *Whole-mount section of fat-wrapped bowel used for morphometry. The antimesenteric subserosal tissues are thickened by fat and the association between transmural inflammation and fat-wrapping is evident*

**Table 3** *Histomorphometric data*

| | Normal | Fat-wrapped | $P^*$ |
|---|---|---|---|
| Mesenteric thickness (mm) | 12·20(6·37) | 30·30(7·91) | <0·01 |
| Internal diameter (mm) | 13·59(3·94) | 8·11(4·36) | <0·05 |
| External diameter (mm) | 21·27(3·11) | 20·56(3·28) | n.s. |
| Wall thickness (mm) | 4·62(1·19) | 7·70(1·87) | <0·01 |
| Muscularis thickness (mm) | 1·91(1·03) | 2·53(0·69) | n.s. |

Values are mean(s.d.). *Student's two-tailed *t* test; n.s., not significant

**Table 4** *Review of 225 small intestinal resections*

| Diagnosis | *n* | Fat-wrapping identified |
|---|---|---|
| Ischaemia or infarction | 77 | 0 |
| Crohn's disease | 58 | 31 |
| Meckel's diverticulum | 25 | 0 |
| Secondary carcinoma or melanoma | 21 | 0 |
| Malignant lymphoma | 13 | 0 |
| Perforation (various causes) | 11 | 0 |
| Radiation enteritis | 5 | 0 |
| Carcinoid* | 4 | 0 |
| Other | 11 | 0 |

*One case showed mesenteric thickening but no fat-wrapping

previous surgery ensured that serosal tissues were not assessable. In only two cases of intestinal Crohn's disease was there an unexplained absence of fat-wrapping.

Morphometric results are shown in *Table 3*. Mesenteric thickness and wall thickness in fat-wrapped areas were significantly greater ($P < 0·01$), while the internal diameter was significantly less ($P < 0·05$). External diameter and muscularis propria thickness were not significantly different between normal and fat-wrapped intestine.

The retrospective review of 225 small bowel resection specimens (*Table 4*) demonstrated histological evidence of fat-wrapping in only 31 cases, in all of which a diagnosis of Crohn's disease could be made on the pathological features present. One resection specimen performed for metastatic carcinoid tumour of the ileum showed mesenteric thickening but no fat encroachment.

## Discussion

The recognition of Crohn's disease by the surgeon at laparotomy relies on serosal changes, luminal restriction and bowel wall thickening. These serosal changes include fat-wrapping with obliteration of the bowel–mesentery angle[6]. When choosing the line of resection the surgeon relies on a clinical assessment of the extent of disease[6]. Histological analysis by frozen section should rarely, if ever, be used in this situation[7]. The surgeon identifies the proximal level of involvement by palpation of the mesenteric margin, enlargement of which is related to bowel wall thickening and to fat-wrapping. Accurate analysis of changes in the mesentery, particularly fat encroachment, is therefore an important part of the surgical assessment of the intestine in Crohn's disease[6].

The present study has demonstrated that fat-wrapping is common in both small and large intestinal Crohn's disease. While it occurs specifically in areas of active transmural inflammation and ulceration, there is by no means exact correspondence, and this is potentially misleading for the surgeon at the time of laparotomy. If the surgeon uses only these subserosal changes upon which to select the margins of excision, then it is possible that the anastomosis will include active, albeit superficial, disease. The significance of such disease at an anastomosis has been a source of controversy[8–15]. Recurrent disease develops within 1 year of resection[14], so it seems logical that active inflammation and ulceration at a margin may increase the likelihood of recurrence. Therefore, the surgeon should not rely entirely on assessment of fat-wrapping and mesenteric thickness in establishing the margins of excision as these do not reflect the full extent of mucosal ulceration.

The present morphometric findings demonstrate that there is true hypertrophy of fat in that there is no evidence of bowel wall shrinkage in the presence of increased mesenteric thickness. Fat-wrapping did not correlate with duration or extent of disease in this study, but in all of these cases there was well established transmural disease for which surgery was necessary. As transmural inflammation is a sequel of ulceration[16] and fat-wrapping probably occurs in response to transmural inflammation, it is reasonable to regard fat-wrapping as an established and more chronic pathological feature of the disease. Its pathogenesis can only be speculated upon. The close correlation with transmural inflammation in the form of lymphoid aggregates would suggest that fat-wrapping is the direct result of release of cytokines from lymphoid tissue.

The retrospective review of small intestinal resections suggests that fat-wrapping is a feature peculiar to Crohn's disease. Some caution must be applied to such a retrospective analysis. Assessment of the mesenteric tissues depends on tissue selection: blocks would not have been selected specifically to demonstrate serosal and subserosal disease. Nevertheless they would have been taken from areas of active disease, strictures, transmural inflammation and ulceration. There was evidence of fat-wrapping in more than half of the cases of Crohn's disease but it was never seen in other conditions. One might expect to observe fat-wrapping in intestinal tuberculosis because of its pathological similarities to Crohn's disease. Even those with much experience of this disease have never observed fat-wrapping in intestinal tuberculosis (D. H. Wright, personal communication). Fat-wrapping has also not been described in other chronic granulomatous enteritides such as yersiniosis.

In conclusion, fat-wrapping has been observed only in Crohn's disease. In cases where some of the pathological features of Crohn's disease, such as fissuring, ulceration and transmural inflammation, are absent[2,17,18], or in acute fulminant colitis when it may be impossible to differentiate between ulcerative colitis and Crohn's disease[19], demonstration of the connective changes that occur in intestinal Crohn's disease may be helpful in the pathological diagnosis of this condition. The surgeon may confidently use fat-wrapping to diagnose Crohn's disease, but should not rely solely on this sign to determine the limits of resection.

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# Zinc-deficient diet impairs adaptive changes in the remaining intestine after massive small bowel resection in the rat

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*An investigation was conducted on the influence of the presence of zinc in an elemental diet on the mucosa of residual intestine after massive small bowel resection. A total of 34 male Sprague–Dawley rats were divided into five groups: control animals* (n = *10*) *were killed after overnight fasting; a second group* (n = *14*) *underwent massive small bowel resection preserving 10 cm of terminal ileum, and the third group* (n = *10*) *underwent sham operation. Animals in the second and third groups were fed either a commercially available elemental diet or a zinc-deficient diet for 2 weeks; they were then killed. In animals receiving the zinc-deficient diet, a significant decrease* ($P < 0{\cdot}05$) *was noted in plasma zinc and total protein, and in mucosal wet weight* (*duodenum*), *thickness* (*duodenum and ileum*), *and protein* (*duodenum*) *and DNA* (*duodenum*) *content. Mucosal sucrase and maltase specific activities in the duodenum and ileum fell but diamine oxidase levels did not. These results suggest that zinc plays an important role in intestinal adaptation in the rat, and indicate that this trace element is essential for intestinal mucosal preservation in this animal.*

The small intestine has the capacity to compensate for loss of absorptive surface area following massive resection[1,2]. The presence of luminal nutrients[1–3] is known to play a role in providing a stimulus for intestinal epithelial growth. Fat[4,5], carbohydrates[6], protein, glutamine[7,8] and micronutrients such as zinc have all been proposed as luminal stimulants.

Gastrointestinal diseases or disorders such as Crohn's disease, short bowel syndrome and gastrointestinal fistula are often associated with severe malabsorption[9,10], and patients with these conditions are at great risk of developing zinc deficiency[11], since zinc homoeostasis is controlled primarily by the gastrointestinal tract[12]. This micronutrient is known to be associated with a wide variety of physiological and biochemical functions, and almost 200 different zinc metalloenzymes including carbonic anhydrase, alkaline phosphatase and DNA and RNA polymerases[11,13] have been identified. Mills *et al.*[14] suggested that the primary site of action of zinc must be in tissue with an extremely high turnover rate, such as intestinal mucosa[1]. This hypothesis was tested in this study. Massive small bowel resection was performed in experimental animals, and the effects of the presence or absence of zinc in the diet on the adaptive changes of the residual intestine were examined.

## Materials and methods

A total of 34 male Sprague–Dawley rats (Oriental Yeast, Osaka, Japan) weighing 200 g were placed in cages and acclimatized to laboratory conditions for 1 week before the experiment. After overnight fasting, the rats were randomly divided into five groups. Ten rats were killed immediately and served as controls; 14 animals underwent resection of the small bowel leaving a 10-cm segment proximal to the ileocaecal junction (resection group). Bowel continuity was restored by end-to-end anastomosis using interrupted 6/0 nylon sutures. The remaining ten animals (sham group) underwent transection of the ileum 10 cm proximal to the ileocaecal junction, which was reanastomosed in the same fashion as for the resection group. The two operated groups were further subdivided to receive a diet either deficient in (Zn−) or supplemented with (Zn+) zinc.

All rats had a feeding gastrostomy tube inserted, which was tunnelled subcutaneously to exit between the scapulae and protected by a harness with a spring coil connected to a swivel. The tube was connected to an infusion pump and enteral nutrient solution was administered continuously throughout the experimental period. The volume and concentration of the diet are shown in *Table 1*. No oral intake was allowed during the experiment and to prevent coprophagy the rats were housed in a cage with a wire mesh floor. Meticulous care was taken during all procedures to avoid contamination with zinc from the environment or materials used in the experiment.

Seven rats undergoing resection and five sham operated animals received a commercially available elemental Zn+ diet (Elental; Ajinomoto, Tokyo, Japan) (*Table 2*). This diet was diluted with tap water and was prepared daily. The zinc concentration in the final

**Table 1** *Schedule of administration of the elemental diet*

| Day | Concentration (%) | Volume ($\mathrm{ml\ kg^{-1}\ day^{-1}}$) | Calorie content ($\mathrm{kcal\ kg^{-1}\ day^{-1}}$) |
|---|---|---|---|
| 0 | 0 | 150* | 0 |
| 1 | 50 | 150 | 75 |
| 2 | 50 | 150 | 75 |
| 3 | 75 | 150 | 113 |
| 4 | 75 | 150 | 113 |
| 5 | 100 | 150 | 150 |
| 6 | 100 | 200 | 200 |
| 7 | 100 | 250 | 250 |
| 8–14 | 100 | 250 | 250 |

*Saline solution

**Table 2** *Composition of Zn+ elemental diet*

| | Concentration (mg per 100 g) |
|---|---|
| Amino acids | 17 659 |
| Carbohydrate | 79 379 |
| Fat | 658 |
| Minerals | 2 086 |
| Vitamins | 42 |
| Zinc sulphate | 9·85 |
| Other | 176 |

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solution for administration was checked daily by flameless atomic absorption spectrophotometry (Hitachi 170-70, Tokyo, Japan). In the Zn+ diet, mean(s.d.) zinc content was 5·95(1·74) $\mu$g ml$^{-1}$. The remaining resected ($n = 7$) and sham operated ($n = 5$) animals were designated Zn− and received the same commercial elemental diet, prepared with a low zinc content (Ajinomoto) and diluted with distilled, deionized water. The final zinc concentration in this diet was 0·11(0·01) $\mu$g ml$^{-1}$.

On the 14th day after operation, animals were killed under ether anaesthesia by exsanguination from the aorta. Plasma was promptly separated. The small intestine was dissected from its mesentery and the duodenum and ileum were divided, washed in cold saline, and a 1-cm segment 4 cm from the anastomosis was taken for histological examination. Mucosal scrapings from the remaining intestine were weighed, homogenized and diluted for measurement of protein by the method of Bradford[15]. Protein content was expressed as milligrams protein per segment. DNA was measured using the method of Prasad *et al.*[16] and expressed as milligrams DNA per segment. Disaccharidase activities (sucrase and maltase specific activities) were assayed according to the method of Dahlqvist[17] and expressed as micromoles glucose produced per minute per milligram protein. Diamine oxidase activity was measured by the method of Yamada *et al.*[18] and expressed as the percentage of the activity obtained for controls.

Data are expressed as mean(s.d.). Body-weight was recorded as the percentage of that on the day of operation. Multiple comparisons were performed after analysis of variance with the Student–Newman–Keuls test[19]. Differences were considered to be significant for $P < 0·05$.

## Results

Plasma zinc levels were significantly lower in the resected Zn− (71·9(10·4) $\mu$g dl$^{-1}$) and sham Zn− (72·7(10·2) $\mu$g dl$^{-1}$) groups compared with control (121·5(9·9) $\mu$g dl$^{-1}$), resected Zn+ (117·1(11·2) $\mu$g dl$^{-1}$) and sham Zn+ (95·8(9·6) $\mu$g dl$^{-1}$) animals.

The animals lost weight in the first week and then began to gain. Final body-weight, expressed as a percentage of the initial value, was not different in the various groups: resected Zn+, 87·4(7·5); resected Zn−, 85·9(6·9); sham Zn+, 89·0(5·8); and sham Zn−, 85·7(6·9).

Plasma total protein levels in sham Zn+ animals (5·7(0·2) mg dl$^{-1}$) did not differ significantly from those of controls (5·5(0·4) mg dl$^{-1}$) but were significantly lower in the resected Zn+ group (4·7(0·3) mg dl$^{-1}$) and in resected Zn− (4·5(0·7) mg dl$^{-1}$) and sham operated Zn− (4·7(0·2) mg dl$^{-1}$) animals.

The mucosal wet weights (*Figure 1*) of duodenum and ileum in both resected groups were significantly increased compared with the other three groups. A significant increase was observed in the duodenum of the resected Zn+ group compared with the resected Zn− group, but this was not seen for the ileum.

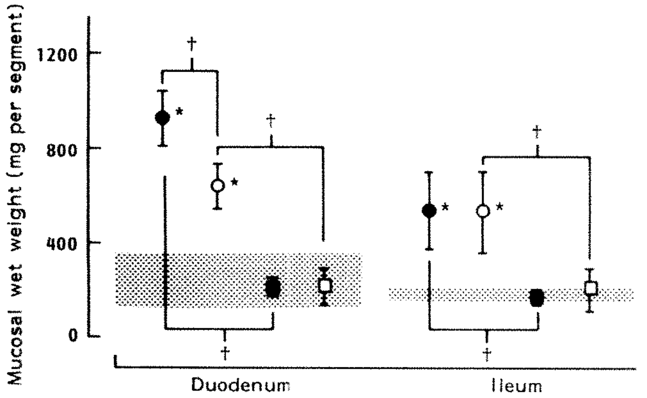

**Figure 1** *Effect of administration of an elemental diet with (Zn+) and without (Zn−) zinc on intestinal mucosal wet weight. Values are mean(s.d.). Results are from the control group (▨) and 2 weeks after sham operation (■, Zn+; □, Zn−) or massive small bowel resection (●, Zn+; ○, Zn−). *P < 0·05* (versus *controls*)*; †P < 0·05 (both Student–Newman–Keuls test)*

Villus height (*Figure 2*) in the duodenum of resected Zn+ animals was significantly increased compared with controls but not compared with resected Zn− animals. Villus height in the resected Zn− group was significantly increased compared with sham operated Zn− animals. Sham operated Zn+ rats showed significantly greater villus height compared with the sham Zn− animals, but there was no difference between these two groups and controls. In the ileum, significant differences were noted between resected Zn+ and sham Zn+ groups and between resected Zn− and sham Zn− animals. In the sham Zn− rats, villus height was significantly less than in controls and in the sham Zn+ group.

No significant difference was noted in duodenal or ileal crypt depth between the control, resected Zn+ and resected Zn− groups. Crypt depth in the duodenum and ileum of sham operated Zn− animals was significantly decreased compared with control and sham Zn+ groups.

As shown in *Figure 3*, the mucosal protein content of the duodenum in the resected Zn+ group showed a significant increase compared with control and sham Zn+ animals. The same change was seen in the resected Zn− rats compared with control and sham Zn− groups. There was also a significant difference between Zn+ and Zn− resected animals. The

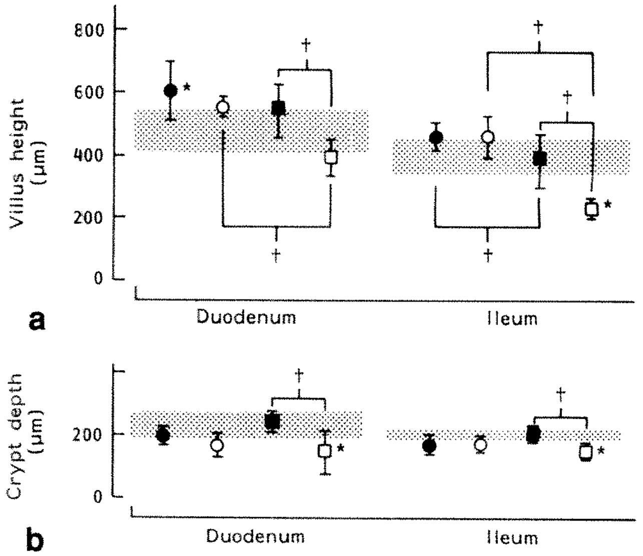

**Figure 2** *Effect of administration of an elemental diet with (Zn+) and without (Zn−) zinc on* **a** *intestinal mucosal villus height and* **b** *crypt depth. Values are mean(s.d.). Results are from the control group (▨) and 2 weeks after sham operation (■, Zn+; □, Zn−) or massive small bowel resection (●, Zn+; ○, Zn−). *P < 0·05* (versus *controls*)*; †P < 0·05 (both Student–Newman–Keuls test)*

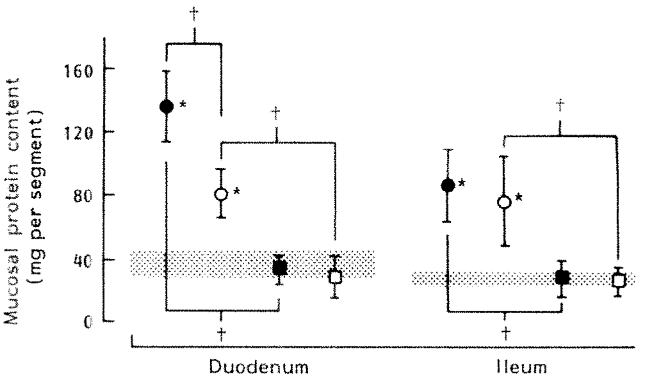

**Figure 3** *Effect of administration of an elemental diet with (Zn+) and without (Zn−) zinc on mucosal protein content. Values are mean(s.d.). Results are from the control group (▨) and 2 weeks after sham operation (■, Zn+; ○, Zn−) or massive small bowel resection (●, Zn+; ○, Zn−). *P < 0·05 (versus* controls*), †P < 0·05 (both Student–Newman–Keuls test)*

mucosal protein contents of the ileum in resected Zn+ and Zn− rats were significantly greater than in the control group, but did not differ from each other. No significant difference was noted between sham operated Zn+ and Zn− animals and controls in either the duodenum or the ileum.

As shown in *Figure 4*, duodenal DNA content was significantly increased in resected Zn+ animals compared with resected Zn− rats and controls. A significant increase was observed in mucosal DNA content in Zn+ and Zn− resected animals compared with sham operated Zn+ and Zn− groups, respectively. Mucosal DNA content in the sham Zn− rats was significantly less than in the control and sham Zn+ groups. In the ileum, there were no significant differences in DNA content.

Activities of maltase and sucrase are shown in *Table 3*. Maltase specific activity in the duodenal mucosa of the resected Zn+ group was significantly higher than that of the control and sham Zn+ animals. Activity of this enzyme was also significantly increased in the resected Zn− group compared with the control and sham Zn− rats. In the ileum of the resected Zn+ group, maltase activity was significantly increased compared with control, resected Zn− and sham Zn+ groups. A significant decrease was observed in the sham Zn− animals compared with the controls and sham Zn+ group.

Sucrase specific activity changed in the same way as that of maltase, although significant differences between resected and sham operated Zn− animals were noted in neither the duodenum nor the ileum.

Diamine oxidase activity in the duodenum showed no significant differences among the various groups (*Table 3*). However, in the ileum, significant decreases were found in the resected Zn+ and Zn− rats compared with sham operated Zn+ and Zn− groups, respectively, and also when compared with controls.

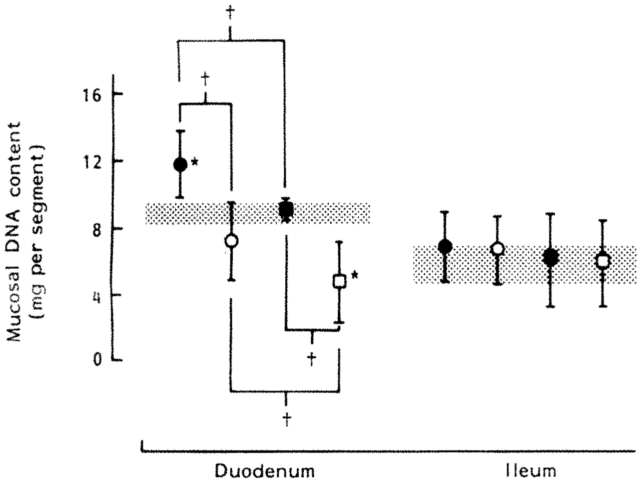

**Figure 4** *Effect of administration of an elemental diet with (Zn+) and without (Zn−) zinc on mucosal DNA content. Values are mean(s.d.). Results are from the control group (▨) and 2 weeks after sham operation (■, Zn+; □, Zn−) or massive small bowel resection (●, Zn+; ○, Zn−).* $*P < 0·05$ *(versus controls);* $†P < 0·05$ *(both Student–Newman–Keuls test)*

## Discussion

It is well known that zinc is essential for protein synthesis[20,21]. Several investigators have reported that zinc deficiency causes growth retardation in animals and humans[22–26]. The intestine may have reduced capacity for nutrient absorption in zinc-deficient states[22,24,27]. The present results show that rats fed a zinc-deficient diet had a significant reduction in plasma total protein and in the protein content of the duodenal mucosa after massive intestinal resection. According to Solomons[28], protein synthesis is highly dependent on the zinc content of RNA polymerase and zinc deficiency may increase the catabolic effect of RNase.

The present study also revealed decreased protein content in enterocytes and a decreased mucosal wet weight in zinc-deficient rats. It appears that mucosal protein is replaced by fat[23,29]. Cytoplasmic accumulation of large lipid droplets in zinc-deficient rats is not a result of either defective triglyceride synthesis or transport out of enterocytes[23], which suggests that it is caused by impaired protein synthesis[23,27]. Besides the impaired protein synthesis, inhibition of DNA synthesis is also reported in zinc-deficient rats[30]. This is most obvious in rapidly proliferating tissues, such as intestinal mucosa[29]. Impaired nuclear division, and thus diminished cell proliferation, would result from deficiencies of DNA polymerase, deoxynucleotidyl transferases and thymidine kinase[28]. In addition, nucleoside phosphorylase, a zinc-containing enzyme in the purine degradation pathway, is known to be zinc dependent[26], which further implicates zinc in the regulation of cell proliferation[28].

The present study showed consistent results with a significant decrease in intestinal mucosal thickness in both the duodenum and ileum of sham operated animals fed a zinc-deficient diet. This decrease can be explained partly by reduced crypt depth. Stem cells are located in this region of the mucosa; this suggests that there is impairment of cell proliferation. Southon *et al.*[31] demonstrated a lower rate of crypt cell division with consequent decreased cell migration into the villi in zinc-deficient animals. However, crypt depth was not decreased in animals undergoing massive resection fed a zinc-deficient diet, so an additional mechanism may act to promote intestinal cell proliferation.

In this study, the effect of dietary zinc on sucrase and maltase specific activity was clearly demonstrated. After massive small bowel resection there was a significant increase in the activity of these enzymes in rats on both diets, but those receiving zinc-deficient nutrition showed a smaller increase. Thus a zinc-deficient diet attenuated the adaptive response to resection, confirming an earlier observation of reduced maltase specific activity in zinc-deficient rats[32]. Zinc deficiency has previously been associated with reduced sucrase activity[22,29], although

**Table 3** *Intestinal enzyme activity*

| | Sucrase (μmol glucose per min per mg protein) | | Maltase (μmol glucose per min per mg protein) | | Diamine oxidase (percentage of control activity) | |
|---|---|---|---|---|---|---|
| Treatment | Duodenum | Ileum | Duodenum | Ileum | Duodenum | Ileum |
| Control | 32·2(12·5) | 24·1(4·1) | 123·8(35·0) | 90·2(9·8) | 100(18·8) | 100(19·7) |
| Resected Zn+ | 176·1(78·0)* | 75·1(47·0)* | 247·9(68·1)† | 159·6(71·5)* | 95(21) | 61(19·9)† |
| Resected Zn− | 72·1(43·0)‡ | 25·0(9·6)§ | 200·2(29·9)‡ | 108·5(20·4)§ | 94(22) | 58(21·3)‡ |
| Sham operated Zn+ | 37·2(21·8)§ | 25·1(13·9)§ | 114·5(20·1)§ | 80·1(15·2) | 96(26) | 91(19) |
| Sham operated Zn− | 8·4(6·4)¶ | 8·0(4·8)¶ | 39·2(23·1)¶ | 55·6(24·0)† | 93(23) | 90(20) |

Values are mean(s.d.). $P < 0·05$: **versus* control, resected Zn− and sham operated Zn+; †*versus* control and sham operated Zn+; ‡*versus* control and sham operated Zn−; §*versus* sham operated Zn−; ¶*versus* control; Student–Newman–Keuls test some authors have found no effect of zinc deficiency on the specific activity of rat intestinal disaccharidases[33–35].

There are several possible explanations for these reductions in disaccharidase activity[22]. First, synthesis of the specific enzyme may be impaired. Second, these enzymes may be zinc metalloenzymes or may be zinc dependent. Third, zinc plays an important role in the maintenance of structure and function of biomembranes. In zinc deficiency, brush border membrane stability, necessary for the function of these membrane-bound enzymes, may be affected. Further studies are necessary to clarify the relationship of zinc and disaccharidase activities.

Diamine oxidase is an enzyme with high activity in the mature cells of the upper villus of small intestinal mucosa and very low activity in all other tissues[36,37]. The location of this enzyme in small intestinal mucosa may reflect the presence of mature functional villus enterocytes[38]. In the present study, there was no significant difference in the duodenal mucosal content of diamine oxidase among the various groups. However, the remaining ileum after massive resection demonstrated approximately 60 per cent of the activity of the preoperative control level; dietary zinc had no effect on this. Erdman *et al.*[39] also reported that diamine oxidase activity fell to 50 per cent in short bowel animals compared with sham operated ones. Such a fall in diamine oxidase activity in the remaining ileum of resected animals could be partly explained by the rapid transit of food directly from the duodenum causing desquamation of ileal mucosa; the level of activity would therefore represent the total villus activity minus the activity of the tip.

In this study, the effect of a zinc-deficient diet on intestinal mucosa was seen as early as 2 weeks, implying that changes occur even during the period of marginal zinc deficiency. Administration of a zinc-deficient diet attenuated but did not eliminate the adaptive response to massive resection. During periods of enteral nutrition, zinc is likely to be an essential trace element for the preservation of intestinal mucosal integrity.

In the short bowel syndrome, enteric fistula and other enteropathies that may be accompanied by massive loss of zinc, plasma zinc levels should be carefully monitored. Supplementation with this micronutrient may be necessary to achieve a favourable outcome.

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## Case report

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# Exteriorization of an ovary: an unusual complication of abdominal drainage

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An unusual complication of abdominal drainage is reported; no similar case has been found in the literature.

### Case report

A 64-year-old obese diabetic woman underwent a radical Pólya gastrectomy for adenocarcinoma of the lesser curvature of the stomach. On the fifth day after surgery the patient developed upper gastrointestinal haemorrhage from a stress ulcer in the gastric remnant. This settled with conservative treatment.

Serous material continued to ooze from a drain in the pouch of Douglas until the 18th day after operation, at which time it was removed. When the drain was removed the right ovary and uterine tube were also pulled out through the defect in the abdominal wall (*Figure 1*). At laparotomy the right ovary and tube were unusually mobile; right salpingo-oöphorectomy was performed.

The patient was discharged 8 days later and continues to be well 6 years after the original operation.

### Discussion

Although abdominal drainage has been used since ancient times, when Celsus employed brass tubes to drain ascites[1], its place in modern surgery is still keenly debated[2]. Most postoperative drains are used prophylactically, to safeguard intestinal anastomoses or to prevent collections of fluid or pus in potential spaces, such as the pouch of Douglas. Ideally, drainage should achieve these aims without adding to the morbidity or mortality of the surgical procedure.

The literature suggests that prophylactic drainage is not beneficial[3]. It has been shown that patients undergoing cholecystectomy[4–6] or splenectomy[7] without subsequent drainage have a lower incidence of complications from bile leakage or infected haematomas than patients with drains. This finding implies that patients who do not have drains inserted are able to resorb most collections that develop.

Studies in animals and humans have shown that the presence of a drain near an anastomosis increases the incidence of anastomotic breakdown following colonic resection[8–12].

The patient reported here highlights a previously unknown complication of abdominal drainage. When the drain in the pouch of Douglas was removed the right ovary was pulled out of the abdominal cavity through the defect in the abdominal wall caused by the drain. This was a consequence of the formation of adhesions between the ovary and drain. It seems probable that such adhesions are more likely to arise when drains are left *in situ* for a long time.

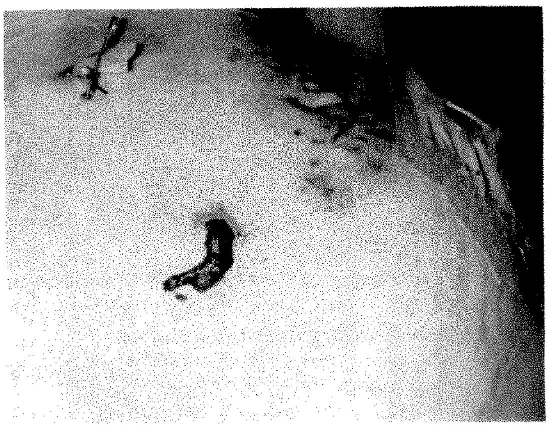

**Figure 1** *The right ovary and fallopian tube lying on the abdomen after removal of the drain*

This unusual complication lends weight to the theory that prophylactic abdominal drainage is not only unhelpful but may even be hazardous. When drains must be used they should be removed as early as possible.

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# Laparoscopy in developing countries in the management of patients with an acute abdomen

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*Surgeons in developing countries see a need to improve diagnosis and decision making in patients with an acute abdomen. Without the benefit of diagnostic aids such as computers and high-resolution ultrasonography, the rate of unnecessary laparotomy is often unacceptably high. The laparoscope is usually available in a developing country and its use easily acquired. Using laparoscopy in doubtful situations the unnecessary laparotomy rate was significantly reduced from 14·0 to 6 per cent* $(P < 0{\cdot}05)$*. Laparoscopy achieved a diagnostic accuracy of 86 per cent and prevented unnecessary laparotomy in 57 per cent of those in whom it was used.*

Unnecessary laparotomy in those with an acute abdomen carries a risk for the patient and increases the duration and cost of hospital stay. Much recent effort has aimed to improve preoperative decision making in this condition[1,2]. Diagnostic methods recently advocated, such as computer-aided diagnosis and high-resolution ultrasonography, are not available in most developing countries. The limited hospital bed space and frequently poor financial status of patients call for more efficient management of resources. Diseases such as ectopic pregnancy and pelvic inflammatory disease, which can be confused with acute appendicitis, are common[3,4] and increase the potential for incorrect diagnosis. This study examines the value of laparoscopy in this situation and compares the results with the records of years before its introduction.

## Patients and methods

The records of all patients undergoing operation with an acute abdomen between 1 April 1985 and 31 March 1989 were retrieved and analysed for clinical presentation, diagnosis, mode of management, timing of operation, operative findings and histological diagnosis.

Between 1 April 1989 and 31 March 1990, patients with an acute abdomen presenting to one surgical team were studied prospectively. Based on clinical assessment and simple investigations such as urine analysis and plain abdominal radiography, the patients were divided into three management options: conservative management (group 1); immediate operative management (group 2); and decision uncertain, signs and symptoms equivocal (group 3).

Patients in group 3 underwent emergency laparoscopy using a KLI laparoscope (KLI, Newton, Pennsylvania, USA). After the procedure patients were subdivided into groups 3A (conservative management chosen) and 3B (immediate laparotomy necessary). All material obtained at surgery was examined by a pathologist.

Statistical analysis was carried out using Student's $t$ test.

## Results

A total of 554 operations were performed during the 4-year retrospective period. Diagnoses in these patients had been achieved by analysis of clinical features and simple laboratory investigations. The commonest operations were appendicectomy (35·4 per cent), and laparotomy for intestinal obstruction (30·3 per cent) and abdominal trauma (16·4 per cent) (*Table 1*). During the 1-year prospective period, 92 patients with an acute abdomen were referred to one surgical unit. The preoperative diagnoses based on similar clinical analysis are shown in *Table 1*.

Of 424 case files available for the retrospective study, 378 contained information (e.g. histopathology results) allowing a final diagnosis. *Table 2* shows the degree of diagnostic inaccuracy during this period. Most unnecessary operations were appendicectomies and laparotomies for blunt abdominal injury. Others included laparotomies for advanced abdominal malignancy (three patients), no pathological findings at surgery (three), pelvic inflammatory disease (two) and peritonitis from umbilical stump sepsis in one infant. The overall rate of unnecessary laparotomy during this period was 14·0 per cent.

Of 92 patients in the prospective study, conservative management was chosen in eight (group 1), immediate laparotomy in 63 (group 2), and in 21 patients the decision was uncertain (group 3).

All patients in group 1 did well. Three patients in group 2 underwent unnecessary surgery: two appendicectomies and one laparotomy for hepatic schistosomiasis.

**Table 1** *Causes of acute abdomen*

| | No. of patients | |
|---|---|---|
| Diagnosis | 1985–1989 | 1989–1990 |
| Acute appendicitis | 196 (35·4) | 40 (43) |
| Intestinal obstruction | 168 (30·3) | 21 (23) |
| Abdominal trauma | | |
| Blunt | 70 (12·6) | 8 (9) |
| Penetrating | 21 (3·8) | 1 (1) |
| Perforated typhoid enteritis | 29 (5·2) | 5 (5) |
| Unknown after laparotomy | 27 (4·9) | 0 (0) |
| Miscellaneous causes | 25 (4·5) | 9 (10) |
| Perforated peptic ulcer | 18 (3·2) | 2 (2) |
| Unknown | 0 (0) | 6 (7) |
| Total | 554 (100) | 92 (100) |

Values in parentheses are percentages

**Table 2** *Unnecessary laparotomies performed during the retrospective period*

| Diagnosis | No. analysed | Unnecessary laparotomy | Unnecessary laparotomy rate (%) |
|---|---|---|---|
| Acute appendicitis | 118 | 35 | 29·7 |
| Intestinal obstruction | 120 | 0 | 0 |
| Abdominal trauma | | | |
| Blunt | 49 | 9 | 18 |
| Penetrating | 16 | 0 | 0 |
| Perforated typhoid enteritis | 21 | 0 | 0 |
| Perforated peptic ulcer | 16 | 0 | 0 |
| Other | 38 | 9 | 24 |
| Total | 378 | 53 | 14·0 |

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**Table 3** *Effect of laparoscopy on the diagnosis and management of 21 patients in group 3*

| Working diagnosis | No. | Laparoscopic diagnosis | No. | Histopathological diagnosis | No. |
|---|---|---|---|---|---|
| Acute appendicitis | 18 | Acute appendicitis | 4* | Acute appendicitis<br>Normal appendix | 3<br>1 |
| | | None (appendix not visualized) | 2* | Acute appendicitis | 2 |
| | | Pelvic inflammatory disease | 9† | | |
| | | Premenstrual pelvic congestion | 2† | | |
| | | Ruptured right tube in bilateral tubal gestation | 1* | Bilateral tubal gestation | 1 |
| Blunt abdominal injury | 1 | Bruising of peritoneum of anterior abdominal wall | 1† | | |
| Acute abdomen (cause unknown) | 2 | *Armillifer armillatus* infestation | 1† | | |
| | | Unknown | 1‡ | | |

Following laparoscopy *seven patients underwent laparotomy (group 3A) and †13 were managed conservatively (group 3B); ‡one patient died while being resuscitated for laparotomy. One of the nine patients with a laparoscopic diagnosis of pelvic inflammatory disease had a chronic right tubal gestation that was missed

**Table 4** *Complications of unnecessary laparotomy during the two periods*

| | 1985–1989 ($n = 53$) | 1989–1990 ($n = 4$) |
|---|---|---|
| Deaths | 6 | 0 |
| Morbidity | 9 | 1 |
| Wound infection | 7 | 1 |
| Postoperative pneumonia | 2 | 0 |
| Unmasking of latent hypertension | 1 | 0 |

**Table 5** *Cost of unnecessary laparotomy*

| | 1985–1989 ($n = 53$) | 1989–1990 ($n = 4$) |
|---|---|---|
| Total hospital bills (naira)* | 22750 | 1535 |
| Mean cost per patient (naira)* | 429·2 | 383·8 |
| Total duration of hospital stay (days) | 397 | 14 |
| Mean duration of hospital stay (days) | 7·5 | 3·5 |

*Seventeen naira are equivalent to £1. The average operation fee over this period was 300 naira for laparotomy and 200 naira for appendicectomy. The average admission fee was 6 naira per day. The rest of the charge is cost of drugs, infusions, dressings etc.

*Table 3* shows the effect of laparoscopy on the management of patients in group 3. Twelve laparotomies were correctly avoided and one was delayed.

One of the seven patients in group 3A underwent an unnecessary appendicectomy.

The rate of unnecessary laparotomy during the prospective period was 6 per cent. The unnecessary appendicectomy rate was 11 per cent and there was no unnecessary laparotomy for blunt abdominal injury.

*Table 4* compares the complications of unnecessary surgery during the two periods. During the retrospective period, nine operations had been delayed longer than 24 h owing to equivocal symptoms and signs, with a mortality rate of 33 per cent. These were laparotomies for perforated peptic ulcer (three patients), perforated typhoid enteritis (two), ruptured tubal pregnancy (one), intussusception (one), strangulated femoral hernia (one) and torted ovarian cyst (one). One laparotomy for chronic tubal gestation was delayed during the prospective study, with no mortality.

*Table 5* shows the cost of admission and surgery, and the duration of hospital stay in patients who underwent unnecessary laparotomy.

The overall mortality rate (including those who were managed conservatively and those who had necessary laparotomy) was 13·4 per cent during the retrospective period and 5 per cent during the prospective period. Overall morbidity rates were 21·2 and 1·1 per cent respectively. Morbidity during the first period included wound infections (17·7 per cent), superficial wound dehiscence (1·4 per cent), burst abdomen (0·5 per cent), postoperative pneumonia (2·6 per cent), faecal fistula (0·9 per cent) and unmasking of latent hypertension (0·2 per cent). During the second period morbidity included wound infections (4 per cent), intestinal obstruction from adhesions (1 per cent), postoperative pneumonia (2 per cent), hepatitis (1 per cent) and malaria (3 per cent).

## Discussion

Unaided clinical diagnosis of the acute abdomen may lead to a high unnecessary laparotomy rate. This is unacceptable: it puts the patient at increased risk and there are various aids to improve diagnosis and decision making[1,2].

Most unnecessary laparotomies during the retrospective period in this study were appendicectomies and laparotomies for blunt abdominal trauma. This was the result of the unreliability of clinical features in these conditions. There was high diagnostic accuracy for intestinal obstruction because of the typical clinical presentation and reliability of plain abdominal radiography. Most delayed operations were for perforated peptic ulcers because of unreliability of presentation and inadequate diagnostic facilities. Unnecessary operations carried a lower mortality rate than delayed surgery. The cost of unnecessary surgery was considerable and these operations caused 10 per cent of the total mortality and morbidity from the acute abdomen during the period. The patients spent a total of 397 days in hospital.

During the prospective study, the rate of unnecessary laparotomy in two other surgical teams where unaided clinical diagnosis of the acute abdomen was practised was 12 per cent. By using the laparoscope that was available from the obstetrics and gynaecology department, the unnecessary laparotomy rate was reduced from 14·0 to 6 per cent after a period of training. Laparoscopy achieved a diagnostic accuracy of 86 per cent and spared unnecessary laparotomy in 57 per cent of those in whom it was used. These 12 patients were saved about 3000 naira (£180), 30–50 days of admission, and potential complications. Three-quarters of these patients had pelvic inflammatory disease, a condition that may be confused with appendicitis, particularly in an environment where both are common.

Laparoscopy prevented delayed laparotomy in a patient with bilateral tubal gestation presenting with features suggestive of acute appendicitis. Without laparoscopy this patient would probably have undergone a gridiron incision for appendicectomy and the left tubal pregnancy might have been missed.

The missed diagnosis of a chronic right tubal gestation was caused by extensive pelvic adhesions surrounding it. If there is incomplete visualization of the peritoneal cavity then patients proceed to a period of observation or laparotomy depending on their condition Ultrasonography, which is available in very few centres (where its use is dominated by the large numbers of patients attending for antenatal care), may also help in evaluating such patients.

The significant reduction in the mortality and morbidity rates in the prospective period resulted from a combination of improved facilities for medical care and a reduction in the unnecessary laparotomy rate

As Paterson-Brown and Vipond[1] stated in 1990, those surgeons 'who are not pursuing routines (to reduce unnecessary surgery) are failing to deliver an adequate service to the patient with acute abdominal pain' For the surgeon working in a developing country, careful clinical evaluation and laparoscopy may be the cheapest and most practical routine. Laparoscopy is most useful in patients with suspected appendicitis and in blunt abdominal trauma when the indications for laparotomy are equivocal.

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# Non-steroidal anti-inflammatory drugs and appendicitis in patients aged over 50 years

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*In a retrospective study 84 patients aged $\geqslant 50$ years undergoing emergency appendicectomy were matched for age and sex with 84 randomly selected emergency admissions as controls. Of the former, 31 (37 per cent) were taking non-steroidal anti-inflammatory drugs (NSAIDs) at admission, compared with nine (11 per cent) of the controls* ($P < 0{\cdot}01$)*. In the study group a suppression of the white cell count was identified on admission in those taking NSAIDs (mean $11{\cdot}9 \times 10^9\ l^{-1}$) compared with those not (mean $14{\cdot}8 \times 10^9\ l^{-1}$)* ($P = 0{\cdot}007$)*. This is the first reported association between appendicitis and NSAIDs. The relative risk by odds ratio was substantially increased at 6·5 (95 per cent confidence interval 2·1–8·8). An NSAID-related impairment of host defences leading to failure in the resolution of inflammatory episodes may explain this association. It is further postulated that the suppression of the white cell response may be a marker of such an effect.*

The adverse effects of non-steroidal anti-inflammatory drugs (NSAIDs) on the upper gastrointestinal tract have been extensively studied. Attention has recently focused on the lower gastrointestinal tract and an association between NSAID therapy and complicated diverticular disease has been demonstrated[1,2]. This paper reports a retrospective case–control study of NSAID intake and appendicitis in patients aged $\geqslant 50$ years.

## Patients and methods

Scottish Morbidity Return data were used to identify patients aged $\geqslant 50$ years who had undergone appendicectomy in Aberdeen Royal Infirmary in the 4-year period between August 1984 and August 1988 The case notes were obtained and the clinical, operative and pathological findings extracted Patients undergoing appendicectomy with no pathological evidence of acute appendicitis were excluded. Drug therapy on admission, initial white cell count, duration of hospital stay and mortality were recorded.

Again from the morbidity return data, the unit number and date of birth of 2000 patients aged $\geqslant 50$ years admitted to this hospital as emergencies between August 1984 and 1988 were obtained. The sex-matched patient nearest in date of birth to each study patient was selected as a control, the ages matched to within 4 years in each case. Again, case notes were scrutinized and drug therapy at the time of admission noted. The quality of the clinical records for both study and control groups was found to be consistent.

Statistics were calculated using Oxstat II (Microsoft UK, Wokingham, UK) and CIA (Professor M J. Gardner and The British Medical Association, London, UK)

## Results

Ninety-one patients were identified; for three the case records were not available, for two they were incomplete and for two, despite coding as appendicitis, histological analysis was not confirmatory. The age range in the remaining 84 patients was 50–91 (median 61) years. Of the 84 patients with appendicitis, 31 (37 per cent) were taking NSAIDs at the time of admission compared with nine (11 per cent) of the controls. The relative risk by odds ratio of being on NSAID therapy at the time of appendicectomy if aged $\geqslant 50$ years was 6·5, with a 95 per cent confidence interval (c.i ) of 2·1–8·8 ($P < 0{\cdot}01$, McNemar's test for paired nominal data).

In the study group three (10 per cent) of the 31 patients taking NSAIDs died in hospital compared with one (2 per cent) of the 53 non-takers. The relative risk of death in patients with appendicitis who were taking NSAIDs was 2·1, with a 95 per cent c.i. of 1·1–4·1 ($P = 0{\cdot}14$, Fisher's exact test).

There was no difference in mean length of stay between patients receiving NSAIDs (10·4 days) and those not (9·0 days) ($P = 0{\cdot}24$, Student's $t$ test). The extent of peritonitis was similar in both groups; 19 (61 per cent) of the 31 takers of NSAIDs had a 'perforated' appendix, as did 31 (58 per cent) of the 53 non-takers. Abscess was found in five (16 per cent) of the 31 takers and in seven (13 per cent) of the 53 non-takers. There was no difference in temperature on admission between the two groups although the mean white cell count on admission in the NSAID takers was significantly lower ($11{\cdot}9 \times 10^9\ l^{-1}$) than in the non-takers ($14{\cdot}8 \times 10^9\ l^{-1}$). The 95 per cent c.i. of this difference was $0{\cdot}8–4{\cdot}9 \times 10^9\ l^{-1}$ ($P = 0\ 007$, Student's $t$ test)

## Discussion

This is the first report of an association between NSAIDs and acute appendicitis. Although it is retrospective, the importance of drug therapy to emergency management, the emergency status of cases and controls, and the involvement of the same pool of resident house officers have maximized the yield and consistency of the data. In contrast, potentially relevant data such as chronicity of drug intake cannot be directly assessed in this way; however, as in a similarly constructed study on diverticular disease[2], information on indication was generally available in the case notes. The indications closely resemble those previously reported, with the majority of patients having evidence of a specific and chronic complaint (most commonly osteoarthrosis). Chronic ingestion of NSAIDs with their symptom-relieving properties is strongly implied.

The findings bear comparison with those of two recent studies of colonic diverticular complications and NSAID use[1,2]. The relative risk of being on NSAID therapy in patients undergoing appendicectomy for appendicitis was 6·5 for patients aged $\geqslant 50$ years. This is a higher risk than that found in the analogous study of colonic diverticular complications requiring surgery[2] (odds ratio 4·0, 95 per cent c.i. 1·5–13·6). Wilson *et al.*[1], in a prospective study of colonic diverticular complications, found that 31 of 92 patients (34 per cent) were taking NSAIDs compared with only 4 per cent in a general practice-based control group.

The emergency hospital admissions used as controls in this

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and the analogous study on diverticular disease give a much higher incidence of NSAID therapy (11 per cent in appendicitis controls and 18 per cent in diverticular disease controls). NSAID intake increases with advancing age[1]; the median age of the patients with appendicitis was 61 years and in the analogous patients with diverticular disease 71 years. This alone could account for the differing rates of NSAID consumption in these two control groups. Langman *et al.*[3], in their study of small and large bowel perforation and haemorrhage, quoted control NSAID intake in 9·3 per cent of hospital patients aged >40 years and 10 per cent of general practice patients aged >60 years. It is unlikely that the control intake in this study is an underestimate and it may be that the relative risk as assessed in the general population is even higher.

In this study, as in the equivalent study of colonic diverticular disease, a minority of patients (13 and 15 per cent respectively) were taking NSAIDs for a systemic disorder such as rheumatoid disease. These cases were equally distributed between the study and control groups and if excluded do not alter the conclusions. It is worthy of note that all studies show a relative risk of adverse effects in the large intestine in association with NSAIDs which is in excess of that commonly quoted for upper gastrointestinal tract perforation or bleeding[3,4].

There was no difference in complication rate or duration of hospital stay between the two groups but the hospital mortality rate was higher in NSAID takers, with a relative risk of 2·1 (95 per cent c.i. 1·1–4·1). This association requires confirmation. *In vitro* white cell function, including bactericidal activity, can be significantly altered in patients taking NSAIDs[5,6]. The observation that the white cell response to insult *in vivo*, as measured by the total white cell count, may be suppressed has not previously been made. Although there was no difference in the frequency of perforation or abscess formation between takers and non-takers of NSAIDs, the white cell count was significantly suppressed in the former group.

Catarrhal inflammation can occur in the appendix but may not lead to appendicectomy if resolution occurs. Impairment of the inflammatory response may influence the outcome of such episodes and so increase the frequency of appendicectomy. It is postulated that the high rate of NSAID ingestion among patients aged ≥50 years undergoing appendicectomy for appendicitis may be related to alteration in host defences. The suppression of white cell response and increased mortality rate in this study may be crude markers of this effect.

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# British Association of Endocrine Surgeons Abstracts

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*Abstracts from the British Association of Endocrine Surgeons Meeting, Canterbury, UK, 14–15 May 1992.*

## Thyroid neoplasia coexistent with chronic lymphocytic thyroiditis

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Chronic lymphocytic thyroiditis (CLT) is common: approximately 140 patients from north-east Scotland (population 500000) are registered annually on the Scottish Automated Follow-up Register.

Between 1985 and 1990 a cytological diagnosis of CLT was made in 82 patients referred with thyroid enlargement. Of 23 patients with histological examination, 14 had neoplasms (lymphoma, six, papillary carcinoma, four; follicular carcinoma, one; follicular adenoma, three), an incidence of 17 per cent (malignancy 13 per cent) The indications for operation (22 patients) or large-needle biopsy (one) were suspicious cytology (in addition to CLT) in 12 patients and clinical suspicion in eight; three patients underwent surgery because of their symptoms or because they wished the swelling removed. All patients with carcinoma or adenoma had either isolated or dominant swellings and in the five with carcinoma cytology was reported as possibly neoplastic. There were no particularly suspicious cytological features in five of six lymphomas. Increasing size of the thyroid swelling was invariable.

The clinical features of thyroid swellings attributable to neoplasia and CLT are similar and cytological or serological evidence of CLT should not lead to complacency Fine-needle aspiration cytology is helpful in detecting carcinoma, but is unreliable in excluding lymphoma

## Changing trends in thyroid cancer

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The relative incidence of histological subtypes of thyroid carcinoma at St Vincent's Hospital between 1970 and 1991 was reviewed. Outcome was assessed and compared with previous reports between 1946 and 1970. Patients with thyroid carcinoma from 1970 to 1991 were identified and pathological and clinical data retrieved

Of 141 patients, 113 were female and 28 male. Incidence of carcinoma was as follows. 57 patients had papillary, 41 follicular, 24 anaplastic and six medullary carcinoma; there were ten lymphomas and three thyroid metastases. The 10-year actuarial disease-free survival rate for papillary carcinoma was 93 per cent, follicular carcinoma 80 per cent and medullary carcinoma 37 per cent The median overall survival for anaplastic carcinoma was 5 months The mean number of patients seen increased from 2·2 per year between 1946 and 1965 to 7 6 per year between 1982 and 1991 From 1946 to 1991 the relative incidence of papillary carcinoma increased from 19 to 57 per cent

Over the period a significant change in the relative incidence of the histological subtypes was observed. follicular carcinoma is associated with endemic goitre and increased iodine intake may explain its reduced incidence Iodine intake in Ireland has increased since the 1960s[1]; there is a need for a national tumour registry to see whether this local trend is reflected nationally

1 Smyth PPA, Hetherton AM, O'Carroll D *et al.* Iodine intake in Ireland – an update *Ir J Med Sci* 1988; **157**· 377–9.

## Papillary thyroid carcinoma revealed by metastatic cervical lymph nodes

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Between 1976 and 1991, 567 patients underwent operation for papillary thyroid carcinoma (PTC)

Twenty-four patients (4 2 per cent) had a cervical lymph node as the sole presenting sign, and in every patient the thyroid gland was clinically normal on initial evaluation. These cervical lymph nodes proved to be metastatic PTC Diagnosis was based on lymph node biopsy.

Metastatic cervical lymph nodes were located in the lateral neck in 87 5 per cent of patients and in the central neck in 12 5 per cent PTC was located in the upper poles in 67 per cent All tumours presented signs of invasion: encapsulated type of capsule invasion (six patients); non-encapsulated sclerosing type (eight), and infiltrative type (ten). The mean size of PTC was 8 mm.

All patients underwent total thyroidectomy and modified neck dissection. Intraglandular dissemination was present in 66 6 per cent of patients During surgery 21 patients were found to have additional metastases to cervical nodes Adjunctive treatment consisted of ablative $^{131}$I therapy and suppression with L-thyroxine. Morbidity and mortality rates in this series were zero, and no distant metastases were discovered With a mean follow-up of 6 years no recurrence has been observed and all the patients remain disease-free.

The following conclusions may thus be drawn PTC revealed by metastatic cervical lymph nodes is rare; these metastatic lymph nodes are usually located in the lateral neck and PTC in the superior pole of the thyroid, since PTC may present signs of invasion such as intraglandular dissemination and additional metastatic lymph nodes are found in 81 per cent, total thyroidectomy, ipsilateral neck dissection and central neck dissection are justified

## Pregnancy and epidermal growth factor receptors in treated papillary thyroid carcinoma

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Approximately 50 per cent of differentiated thyroid cancers in women present during their child-bearing years The literature suggests that pregnancy does not alter its clinical course for those thought to be adequately treated by surgery and thyroid-stimulating hormone (TSH) suppression or those known to harbour residual disease Examples of thyroid cancer recurrence related to pregnancy have been described and there is doubt whether pregnancy may be detrimental[1]

A 23-year-old woman presented with a cystic cervical metastatic lymph node from papillary thyroid carcinoma. A 'Crile' type near-total thyroidectomy with node dissection was performed on 6 December 1988 Satisfactory TSH suppression with sodium thyroxine ($T_4$) was achieved She became pregnant and $T_4$ therapy was monitored and increased during her middle and third trimesters On 9 January 1991, because of pre-eclamptic toxaemia, a caesarean section was used to deliver a normal baby girl Thereafter the patient's $T_4$ therapy was adjusted to continue full TSH suppression, but by October 1991 recurrent metastatic nodes were confirmed by fine-needle aspiration, resulting in further node dissection. This metastatic nodal tissue demonstrated epidermal growth factor receptors at levels >20 fmol/l. Such receptors have been recognized in differentiated thyroid cancers and hyperplastic multinodular goitres[2]. Their significance is at present uncertain but could be related to the therapeutic efficacy of TSH suppression.

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2. Msuda H, Sugenoya A, Kobayashi S *et al.* Epidermal growth factor receptor on human thyroid neoplasms *World J Surg* 1988, **12**. 616–22.

## Thyroid cancer: a changing tumour

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A preliminary report on 492 patients with thyroid cancer treated between 1932 and 1972 has been presented A final report (with 380 patients having died by last follow-up in 1988) is presented. Papillary

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carcinoma comprised 34 per cent ($n = 168$), follicular carcinoma 16 per cent ($n = 80$) and anaplastic carcinoma 33 per cent ($n = 162$) of cases. The crude 20-year probability of survival was 54, 29 and 1 per cent respectively.

For papillary carcinoma, excluding non-cancer deaths, the mortality rate was 68 per cent and in those 46 patients who died from cancer 32 had persistent local disease. Age, histology (tumour type), tumour stage and sex exercised significant influence on survival.

The non-follicular cell tumours were lymphoma (7 per cent; $n = 35$), medullary carcinoma (3 per cent, $n = 13$) and fibrosarcoma (1 per cent; $n = 4$). During this period a radical shift from anaplastic to papillary carcinoma took place and medullary carcinoma was recognized.

### Prospective randomized double-blind study of thyroxine suppressive therapy in preventing nodular thyroid recurrence after surgery

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A prospective randomized double-blind trial was carried out to investigate the effectiveness of L-thyroxine ($T_4$) suppressive treatment in preventing recurrence of nodular goitre after surgical treatment. A total of 60 patients with euthyroid nodular goitre were submitted to preliminary ultrasonography to evaluate the sites and dimensions of the nodular goitres. 26 underwent subtotal thyroidectomy, 21 hemithyroidectomy and 13 nodular excision.

After surgery all the patients were randomized to two groups: group 1 consisted of 32 patients who were treated with $T_4$ at substitutive dosage (100 μg/day); group 2 included 28 patients who were submitted to $T_4$ suppressive therapy (2·5–3 μg/kg/day).

Patients were examined every 6 months to evaluate thyroid hormone and thyroid-stimulating hormone concentrations and by ultrasonography to evaluate the recurrence of goitre and/or nodular thyroid lesions.

Patients were evaluated 2 years after surgical treatment. At the end of the follow-up 24 nodular recurrences were seen in group 1 and six in group 2. Statistical analyses ($\chi^2$) revealed a significantly lower frequency of nodular recurrence in group 2 ($P < 0{\cdot}005$). The response to $T_4$ suppressive treatment was better in patients from endemic goitre areas ($P < 0{\cdot}01$), and in those with multinodular goitre ($P < 0{\cdot}01$). No significant difference was present with respect to the type of surgical treatment.

$T_4$ suppressive therapy is effective in the prevention of nodular recurrence after thyroidectomy, especially in patients from endemic goitre areas affected with multinodular goitre.

### Parathyroid carcinoma: review of a 19-year experience

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Parathyroid carcinoma is a rare disease. Between March 1973 and January 1992, eight patients were treated at the University Hospital of Wales. All patients had severe hyperparathyroidism with a mean serum calcium level of 4·01 mmol/l and parathyroid hormone (PTH) levels grossly raised (mean 7·2 times normal). Excised tumour weights ranged from 1·76 to 9·22 (mean 5·22) g. Six patients had sporadic parathyroid carcinoma and two were considered to have familial parathyroid disease without evidence of multiple endocrine neoplasia (MEN) syndrome.

A small number of families have been reported in which familial hyperparathyroidism is associated with a parathyroid adenoma or carcinoma and in which there is no evidence of involvement of any other endocrine gland. Using an assay for intact 1-84 PTH in one family evidence for involvement of three generations by hyperparathyroidism has been found without evidence for involvement of any other endocrine gland, clinically or by prolactin assay in either family.

The pattern of inheritance in these two families is that of an autosomal dominant defect. In these families there were six other members with hyperparathyroidism resulting from adenoma, two affected members of one family had unusual jaw tumours, one of which was an ossifying fibroma. Hyperparathyroidism presented in all involved cases at an early age (mean 33 years compared with a mean of 65·2 years for the sporadic cases). Seven patients are alive and well with mean follow-up of 8·1 years (range 3 months to 18 years). One patient died from metastatic disease and uncontrolled hypercalcaemia.

From this analysis of patients with parathyroid carcinoma it is important to be aware of familial non-MEN parathyroid disease and presentation of parathyroid carcinoma at a young age should alert the clinician to this possibility.

For optimum management and good long-term results the surgeon must recognize the condition and perform an *en bloc* resection at initial surgery. Recurrent hypercalcaemia should be investigated with localization studies and further surgery to resect metastases where feasible.

### Somatostatin treatment for hyperparathyroidism

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Primary hyperparathyroidism is one of the most common syndromes of endocrine overactivity. Medical therapy for hyperparathyroidism is of limited use and calcitonin and diphosphonates do not give good long-term control of disease. This work examines the efficacy of a somatostatin analogue in the management of hyperparathyroidism. Ten patients were admitted before parathyroid surgery for localization procedures. Each was treated for 6 days with subcutaneous Sandostatin (Sandoz, Camberley, UK) at a dose of 100 μg twice each day. At the end of the treatment a fasting blood sample was taken for serum calcium and parathyroid hormone determination. The 24-h urinary calcium level was measured before and at the end of treatment.

All but one patient showed a reduction in 24-h urinary calcium over the 6-day period of treatment (pretreatment median 5·8 (range 1·8–13·5) mmol per sample, post-treatment median 4·15 (range 0·7–13·4) mmol per sample, $P < 0{\cdot}05$, paired $t$ test) and a reduction in calcium·creatinine ratio (pretreatment 0·72 (range 0·37–1·91), post-treatment 0·56 (range 0·06–1·19); $P = 0{\cdot}05$). Eight of the ten patients showed reduced serum calcium levels but these decreases were not statistically significant.

Pretreatment and post-treatment parathyroid hormone levels were available in six patients and although five levels increased following treatment this was not statistically significant.

Sandostatin may provide a therapy for patients with hyperparathyroidism who have undergone unsuccessful neck exploration or who are unfit for surgery. It may ameliorate hypercalciuria and reduce stone formation.

### Multiglandular disease in seemingly sporadic primary hyperthyroidism

C Proye, B. Carnaille, J P Bizard and J L. Quievreux, *Service de Chirurgie Générale et Endocrinienne, Hôpital Huriez, Lille, France*

This study was undertaken to reassess the frequency of multiglandular disease in hyperthyroidism in a recent series and to make the correct decision between unilateral and bilateral neck exploration.

Multiglandular disease has been defined as more than one grossly enlarged gland weighing >50 mg. A rim of normal parathyroid tissue was diagnostic of adenoma.

A total of 918 consecutive bilateral neck explorations for hyperthyroidism were performed. 624 before 1989 and 294 between 1989 and 1991. Grossly enlarged glands were removed and normal-looking ones left untouched. Specimens were weighed and underwent pathological examination. From 1989, oil-red O staining was performed to assess hyperfunction.

Before 1989, the rate of multiglandular disease was 21 per cent, after 1989 it was 17 per cent (51 of 294). Of those 51 cases, 11 were multiple endocrine neoplasias, two were familial metachronous (second) adenoma and 38 seemingly sporadic. There were two triple adenomas, six double adenomas (2·9 per cent rate of true multiple adenomas), 22 adenomas associated with a second hyperplastic gland, five cases of hyperplasia of two glands and three other cases (second 'normal' overweight gland up to 487 mg). With more restrictive criteria (excluding the second enlarged gland if weighing <100 mg and deprived of rim and/or of negative oil-red O staining) there remained 32 cases (i.e. an 11·6 per cent rate of multiglandular disease in sporadic hyperthyroidism). Unilateral exploration had missed 30 of 38 second enlarged glands and various preoperative imaging studies performed in 23 patients demonstrated more than one gland in only four.

Therefore, in sporadic hyperthyroidism, the rate of multiglandular disease is currently 13·8 per cent and routine bilateral neck exploration is strongly recommended.

## $\beta_2$-Microglobulinuria and long-term outcome following curative surgery of primary hyperparathyroidism

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Previous studies in patients with primary hyperparathyroidism have shown changes in renal function detectable by measuring urinary $\beta_2$-microglobulin ($B_2M$) excretion, despite normal conventional renal function tests.

A cohort of 21 patients, mean age 59·8 (range 40–74) years, 15 women and six men, who had undergone curative parathyroidectomy, were studied longitudinally for a mean of 4·2 (range 2·8–5·6) years in terms of blood pressure, renal function and urinary $B_2M$ excretion on 1-h timed urine specimen

Twelve patients were normotensive with normal preoperative renal function, mean serum calcium 3·03 (range 2·47–3·52) mmol/l and urinary $B_2M$ 250 (range 110–420) μg/l. Nine patients either had raised serum creatinine, mean 146·2 (range 124–171) μmol/l, or were hypertensive with diastolic blood pressure >95 mmHg; mean serum calcium 3·13 (range 2·90–3·39) mmol/l and urinary $B_2M$ 589 (range 116–1160) μg/l. Following surgery, the mean serum calcium for all patients fell to 2·51 (range 2·21–2·67) mmol/l and $B_2M$ excretion to <70 μg/l. Preoperative $B_2M$ excretion was significantly higher in the normotensive patients ($P < 0{\cdot}01$, two-tailed $t$ test).

At follow-up, five previously normotensive patients had developed hypertension; their mean preoperative $B_2M$ excretion was 327 (122–420) μg/l whereas the seven who remained normotensive had mean preoperative $B_2M$ excretion of 196 (110–340) μg/l ($P < 0{\cdot}05$). There was a significantly higher $B_2M$ excretion in the group who were initially hypertensive or with raised creatinine compared with those patients who developed hypertension ($P < 0{\cdot}001$)

This preliminary study suggests that the preoperative quantification of $B_2M$ excretion may have a predictive role in the identification of patients who may subsequently develop hypertension despite curative parathyroid surgery.

## Hyperparathyroidism and the intrathyroidal parathyroid gland

C. Proye, B. Carnaille, J.P. Bizard and J.L. Quievreux, *Service de Chirurgie Générale et Endocrinienne, Hôpital Huriez, Lille, France*

This study was undertaken to determine the frequency of intrathyroidal parathyroid glands during surgery for hyperparathyroidism.

A total of 1000 consecutive patients underwent operation for proven or suspected hyperparathyroidism: 806 had proven primary hyperparathyroidism, 138 secondary hyperparathyroidism, 56 questionable cases Forty-one parathyroid glands were found within the thyroid

In 37 patients (3·7 per cent) one or more parathyroid glands were intrathyroidal. 15 of 613 uniglandular lesions (2·5 per cent), eight of 193 multiglandular lesions (4·1 per cent), 13 of 136 secondary or tertiary hyperparathyroidism (9·5 per cent) and one of 56 'other' patients. There were two upper parathyroid and 35 lower parathyroid glands. In three patients the gland was a fifth gland Three patients had both lower glands intrathyroid, in only one case were two ipsilateral glands intrathyroidal There were 2·5 times more right than left intrathyroidal glands In ten patients thyroid disease was associated. Preoperative imaging was positive in seven of 11 cases. All glands but one were discovered during a first cervicotomy. In 30 patients the intrathyroidal parathyroid gland was visible on the thyroid surface; in 11 patients the gland was invisible and was discovered by palpation or inside the specimen after blind lobectomy (seven cases). Adenomas and hyperplasia were equally distributed.

Both normal and enlarged parathyroids can be intrathyroidal and invisible without any associated thyroid disease This abnormality is more frequent on the right and affects mainly the lower parathyroids It can be bilateral or involve both ipsilateral glands This possible ectopia may be discovered by routine preoperative thyroid ultrasonography.

## Parallel-hole collimator in isotopic scanning of local recurrent parathyroid malignancy

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Locally recurrent parathyroid carcinoma is a well recognized but rare problem The localization of such tumours before surgical re-exploration allows lateralization of the tumour but provides no detailed data on its position Exploration of the neck with attendant risks to vital vascular and neural structures has been required to ensure clearance of recurrent disease. A novel method for providing detailed preoperative localization of such tumours using a parallel-hole collimator and technetium sestamibi scanning is described Using fixed landmarks an accurate grid reference system can be developed; its use in the management of two patients is described

## Surgery for tertiary hyperparathyroidism

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This study evaluates surgery for tertiary hyperparathyroidism in 35 patients between January 1986 and December 1991. Most patients (24) had renal transplantation carried out before surgery for tertiary hyperparathyroidism. The mean preoperative parathyroid hormone level was 348 pg/l and the mean preoperative calcium level 2·79 mmol/l. A total of 32 patients underwent uneventful primary neck exploration during which half of one parathyroid gland was left in the neck The mean follow-up in these patients was 14·4 months and the mean calcium level at follow-up 2·27 mmol/l.

Three patients were referred with tertiary hyperparathyroidism despite having a mean of two neck explorations before referral Successful neck exploration was carried out in two patients but the third required a mediastinal split to identify a parathyroid adenoma in the left upper chest Three patients developed recurrent hyperparathyroidism (9 per cent) and all three underwent successful removal and forearm autotransplantation of the parathyroid remnant There was no mortality in this series but five patients remain on calcium supplementation for symptomatic hypocalcaemia

Surgery for tertiary hyperparathyroidism carries minimum morbidity and mortality risks. It remains unclear, however, whether primary autotransplantation or leaving a parathyroid remnant in the neck is the correct surgical option

## Percutaneous drainage of adrenal cysts

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Cystic adrenal lesions are rare and usually asymptomatic Surgical treatment is advised according to the size of the tumour mass and the compression of near organs Percutaneous drainage of adrenal cysts is an interesting treatment option.

Over a 15-year period 19 patients with an adrenal cyst were seen After 1982 ultrasonography became the technique of choice for discovering and studying adrenal cysts Computed tomography was performed in the later years to define size and structure of the cystic mass Surgical treatment was proposed initially for large masses Percutaneous drainage of adrenal cysts was performed under local anaesthesia, using the posterior approach The procedure was performed with 21-Fr needles The cyst fluid was aspirated and sent for cytology. In one patient alcoholization of the cyst was attempted by injection of 95 per cent sterile alcohol into the cystic cavity Alcohol was removed after 10 min

In the 19 patients studied 23 adrenal cysts were found Four patients underwent surgical excision of the mass and percutaneous drainage was performed in the remaining patients.

Cysts were completely evacuated and radiography showed the collapse of the adrenal cyst The one lesion treated by alcoholization decreased in size and the patient remains asymptomatic

## Localization and surgical management of insulinoma

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Insulin-secreting tumours of the pancreas are rare and present many diagnostic and therapeutic challenges.

Between 1978 and 1991, 21 patients were referred with a suspected diagnosis of insulinoma (mean age 50 years, female:male ratio 2:1). The diagnosis was confirmed by demonstration of hypoglycaemia with inappropriate hyperinsulinism during supervized fasting. One patient refused surgery.

Selective visceral angiography correctly localized the lesion in 19 of 20 cases; computed tomography was accurate in four of 14. Endoscopic ultrasonography has been used recently with moderate success (three positive cases of six).

At laparotomy, the tumour was located in the pancreatic tail in 11 cases, the body in four and head in three. Multiple tumours were found in one patient and exploration was negative in one; 14 tumours were enucleated and five were removed by distal pancreatectomy. The operative mortality rate was zero. Seven patients had complications (two subphrenic collections which were drained percutaneously, four wound infections, one pulmonary embolus).

Selective angiography was the most accurate localization procedure for insulinoma. With further experience, endoscopic ultrasonography may prove useful as a less invasive localizing procedure. Surgery was curative in 90 per cent of cases with acceptable morbidity and no deaths.

## Surgery for phaeochromocytoma

O L. Beatty, C F.J. Russell, T L Kennedy, D.R Hadden, A L Kennedy and A B. Atkinson, *Endocrine Surgery Unit and Sir George Clark Metabolic Unit, Royal Victoria Hospital, Belfast, UK*

Between 1970 and 1991, 37 patients (20 women, 17 men) underwent primary surgery for phaeochromocytoma, 32 individuals had sporadic tumour (mean age at operation 40 years) and five had phaeochromocytoma as one component of the multiple endocrine neoplasia type 2 syndrome (mean age at operation 38 years). Two patients suffered from multiple neurofibromatosis. Preoperative urinary catecholamine or metabolite levels were elevated in 33 patients and normal in four.

Tumour localization was achieved using computed tomography (25 patients), ultrasonography (four), vascular studies (ten) and, more recently, *m*-iodobenzylguanidine scanning (four). Twenty-two individuals had a unilateral adrenal phaeochromocytoma, nine had bilateral tumours and six patients had extra-adrenal lesions. Surgical approaches included bilateral (14 patients) and unilateral (eight) subcostal, posterolateral with rib resection (seven), thoracoabdominal (five) and paramedian (three). Direct tumour invasion necessitated concomitant nephrectomy in two patients and splenectomy in one.

There was no perioperative mortality. Postoperative complications included atelectasis (four patients), haemorrhage requiring reoperation (two), wound haematoma (three), deep vein thrombosis and a non-functioning kidney.

Tumour recurred in six patients at a mean interval of 4·7 (range 2–10) years from initial surgery, three of these died from metastatic disease 7, 12 and 12 years after first operation.

Patients with phaeochromocytoma can undergo operation safely and successfully in centres with appropriate endocrinological, anaesthetic and surgical interest and experience.

## Hugh Young posterior approach for adrenalectomy: 3 years of experience

H.Y. Chan and N.E Dudley, *Department of General Surgery, John Radcliffe Hospital, Oxford, UK*

Since 1989, 19 consecutive adrenalectomies (seven bilateral and five unilateral) have been performed on 12 patients (ten women and two men). ten with Cushing's syndrome, one Conn's adenoma and one other functioning adenoma. All were performed through the posterior approach. There was no routine antibiotic prophylaxis and a urinary catheter was inserted in only one patient in theatre. Hospital stay averaged 8·75 (range 7–11) days, with some patients subsequently transferring to the endocrine unit for medical assessment. No intensive care facilities were required.

Intraoperative complications included two caval tears (on the right) which were easily repaired. Each patient had individually tailored hormonal cover and there were no significant adverse metabolic sequelae. Other complications comprised five chest infections, three wound infections, one pressure sore, one paralytic ileus, one retention of urine, and one case of renal failure with coliform urinary tract infection.

The posterior approach is safe for most adrenal operations. Routine antibiotic prophylaxis is not required for this procedure in patients with Cushing's syndrome, nor are urinary catheters. Tailoring hormonal cover for each patient has minimized the risk of steroid crises and eliminated this important factor for inexperienced junior surgical staff.

## Adrenocortical carcinomas surgically treated in France

P. Icard, Y Chapuis, B. Andreassian, C. Proye and the French Association of Endocrine Surgeons, *Service de Chirurgie Générale et Endocrinienne, Hôpital Huriez, Lille, France*

This retrospective analysis is based on 156 cases of adrenocortical carcinoma operated on by the members of the French Association of Endocrine Surgeons from 1978 to 1991. There were 95 women and 61 men with a mean age of 47 years. At presentation 55 per cent presented space-occupying symptoms, 19 per cent of adrenocortical carcinomas were incidentally discovered, 52 per cent of patients had functional symptoms. Of the patients, 94 per cent underwent resection and 20 per cent of these had extended resection. Curative resection was achieved in 81 per cent of patients. According to the MacFarlane classification, 5 per cent of tumours were stage I, 48 per cent stage II, 25 per cent stage III and 22 per cent stage IV. Of the patients 13 per cent received mitotane before and 47 per cent after surgery. Of the 128 who underwent curative resection, 41 (32 per cent) experienced local recurrence and 22 underwent reoperation. Metastases occurred in 50 per cent.

Over half (60 per cent) of the patients died; the operative mortality rate was 5 per cent and the late mortality rate 55 per cent after a mean survival of 21 months – 40 per cent of the patients are still alive (12 of 62 with recurrence) with a mean survival of 39 months.

The overall 5-year actuarial survival rate was 34 per cent, 42 per cent for the curative group (53 per cent for local cancer and 24 per cent for stage III). Statistical analysis of survival demonstrated that prognosis was better for patients $<40$ years old ($P < 0{\cdot}05$) and in those with androgen-secreting tumours ($P < 0{\cdot}05$). Non-secreting tumours and precursor-secreting tumours were borderline favourable prognostic factors. Mitotane improved the results in patients with metastases only if they received it after surgery ($P < 0{\cdot}05$ *versus* non-mitotane treated patients).

## Surgical management of adrenal disorders

J G. Geoghegan, M Emberton, D Corry, K Tan, E R T C Owen, S R Bloom and J.A. Lynn, *Departments of Endocrine Surgery and Endocrinology, Hammersmith Hospital, London, UK*

Surgery plays a major role in the management of adrenal disease. Between 1978 and 1991, 83 patients (mean age 42 years, male:female ratio 1:2·3) underwent adrenalectomy. The tumour types were phaeochromocytomas (35 patients), cortical adenomas (21 patients presenting as Cushing's syndrome (eight), Conn's (eight), virilization (two), and non-functioning (three)), cortical carcinomas (nine patients), adrenal hyperplasia (13 patients: three ectopic adrenocorticotrophic hormone, ten uncontrolled Cushing's disease), and miscellaneous tumours (five patients). Localization early in the study period was principally by selective venous sampling. This was superseded by computed tomography (69 patients, with 100 per cent specificity and sensitivity). Isotope scanning correctly identified a phaeochromocytoma in ten of 11 patients.

In 74 patients (89 per cent) the presenting clinical syndrome completely resolved or was substantially improved after surgery. The operative mortality rate was 5 per cent (four patients: three with cortical carcinomas, one phaeochromocytoma) and complications occurred in 16 patients (19 per cent).

Adrenalectomy offers safe and effective treatment for benign adrenal gland disorders. Surgery for adrenal cortical carcinoma is associated with significant operative mortality but offers the only prospect of cure.

# Correspondence

## Laparoscopic appendicectomy

*Sir*

I was delighted to read the excellent Leading Article by Messrs Loh and Taylor (*Br J Surg* 1992; 79 289–90). There is no doubt that laparoscopic appendicectomy is often easier than laparoscopic cholecystectomy, provided the right technical approach is learnt and subsequently developed The difficulty has been that most appendicectomies in this country are performed as an emergency, and in the first few cases the 'learning curve' means that the procedure will take of the order of 1 h 30 min to 2 h and in some units over 4 h This engenders considerable reluctance on the part of theatre staff and hard-pressed surgical staff to fit it in with a busy emergency operating schedule

In addition, there are a number of surgical prejudices that need to be exorcised such as the use of non-absorbable staples in an area of potential infection and the need to bury the appendix stump. Likewise, many surgeons are worried that manipulation of a turgid appendix may precipitate a rupture and cause considerable contamination. Care and technical skill and the use of a plastic bag as mentioned by Loh and Taylor easily solve the problem, and even if the appendix has already perforated it is easy to lavage the peritoneal cavity under direct vision. Equally, there is no doubt that, even though the sum of the incisions for the various ports may exceed a small open incision, recuperation after laparoscopy is much faster and the cosmetic result superior. While it is true that there is some curtailment of hospital stay this is probably marginal as patients with peritonitis still require antibiotic therapy and that often forgotten therapeutic weapon, rest Finally, the long retrocaecal appendix is actually easier to remove laparoscopically than by open surgery when the wound would often have to be extended

The need to try to improve the negative laparotomy rate (which is currently between 15 and 30 per cent), particularly in children and young women with gynaecological problems, is readily met by laparoscopy, which is perfect for diagnostic as well as therapeutic purposes. A considerable number of gynaecological problems can be dealt with laparoscopically and laparoscopic appendicectomy in children is very easy indeed, although great care has to be exercised in obtaining access.

Loh and Taylor suggest a prospective randomized clinical trial, but while this is theoretically desirable the technique has outgrown the necessity, much as with cholecystectomy, provided the surgeon has obtained adequate experience and is not afraid to convert to an open procedure at the first sign of difficulty. My own experience to date numbers over 30 consecutive laparoscopic appendicectomies and compares very favourably with a personal audit of 254 open cases (unpublished data) in every parameter measured including operating time. Provided, therefore, that the technique is learnt to an acceptable standard and specialist supervision is available for emergency cases, there is no justification for a trial that would deny half of the patients the undoubted benefits of a superior technique.

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## The missing appendix

*Sir*

The recent Leading Article on laparoscopic appendicectomy (*Br J Surg* 1992; 79. 289–90) was timely. However, the precise role of diagnostic laparoscopy in patients with a clinical diagnosis of acute appendicitis remains unclear One of the advantages of laparoscopic appendicectomy is that all patients with right iliac fossa pain have a diagnostic laparoscopy. This has been promoted as advantageous because it allows making an alternative diagnosis in those patients in whom the appendix is found to be normal In a prospective study of 120 patients with a clinical diagnosis of acute appendicitis, randomized to undergo laparoscopic or open appendicectomy, we have not found this to be so In patients with a normal appendix, a diagnosis was established through a grid-iron incision just as often as with a laparoscope open appendicectomy ($n = 61$) six 'alternative diagnoses', three 'no diagnosis' compared with laparoscopic appendicectomy ($n = 59$) eight 'alternative diagnoses', two 'no diagnosis' ($P$ not significant). Surgical dogma dictates that if a normal appendix is found at open operation it is removed, apparently because no patient can be trusted to tell a doctor in the future that they have not had their appendix out. An alternative diagnosis made by laparoscopy, however, rarely leads to a normal appendix being removed. We will have to trust patients who have had laparoscopic appendicectomy to tell us their appendix has been removed. The potential pitfalls are illustrated by the following conversation with a 33-year-old patient 2 weeks after undergoing laparoscopic appendicectomy for acute appendicitis. On leaving the outpatient's clinic the patient enquired:

> '*What was wrong with me?*'
> 'Acute appendicitis'
> '*Why didn't you remove my appendix?*'
> 'We did'
> '*But there's no scar!*'

Presumably, but for this last-minute question, this patient would have told any doctor consulted in the future that the appendix was still present. Beware the patient with lower abdominal pain and a 1-cm scar at the umbilicus.

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## Laparoscopic approach to Meckel's diverticulectomy

*Sir*

We read with interest the recent Surgical Workshop on laparoscopic diverticulectomy (*Br J Surg* 1992; 79. 211) and wish to share our experience in this regard Attwood *et al* reputedly described the first laparoscopic approach to performing Meckel's diverticulectomy for acute inflammation. We are currently conducting a study attempting to evaluate the use of laparoscopy in the investigation of obscure intestinal bleeding in paediatric patients in whom upper gastrointestinal endoscopy, colonoscopy and barium studies have all been non-diagnostic Preliminary results have been encouraging In this cohort of children with massive haemorrhagic episodes strongly suspicious of bleeding from a Meckel's diverticulum, we elect to perform laparoscopy irrespective of the technetium scan findings, since the false-negative rate of the latter ranges from 25 to 50 per cent, and false-positive scans are encountered in a wide variety of conditions, some of which might also present with bleeding[1,2].

A 10-mm cannula placed in the folds of the umbilicus is used for the placement of the laparoscope A 5-mm and a 10-mm cannula inserted in the mid-clavicular line on either side of the umbilical port are used for the passage of an Endo-Grasp and an Endo-Babcock (US Surgical, Norwalk, Connecticut, USA), respectively. Successive segments of small bowel held between the forceps are scrutinized, starting from its junction with the caecum. When a Meckel's diverticulum is identified, the Endo-Babcock is removed to allow for the relocation of the laparoscope to its port. The Endo-Babcock is then passed through the umbilical sheath, directed to grasp the tip of the diverticulum, and withdrawn together with the sheath The umbilical incision is extended until the whole diverticulum is delivered through the abdominal wall.

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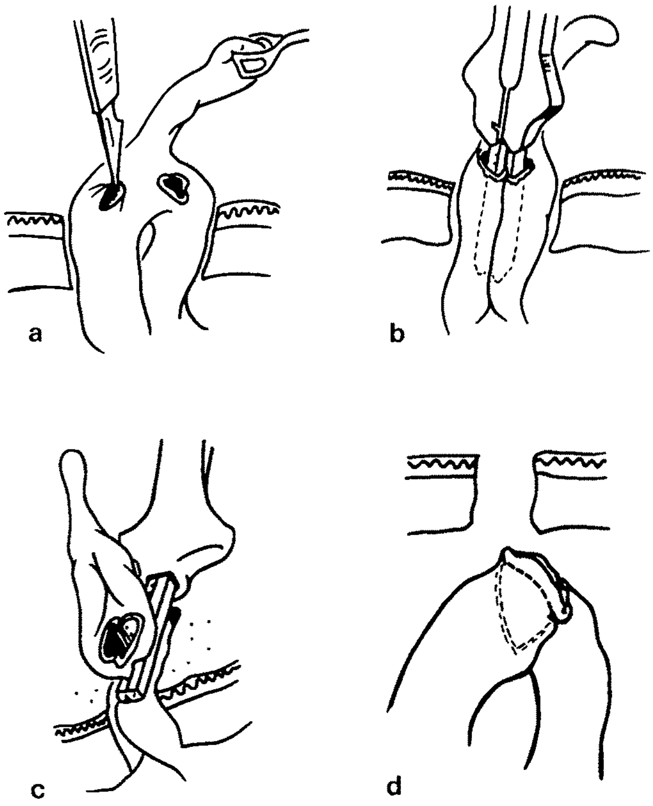

**Figure 1** *Technique of assisted laparoscopic Meckel's diverticulectomy for bleeding complications* **a** *Two small stab wounds are made on either side of the base of the diverticulum which has been eviscerated through the extended umbilical port incision.* **b** *The forks of a GIA stapler are inserted, approximated and fired* **c** *Second application of the stapler placed at right angles to the first helps resect the diverticulum and adjacent ileum bearing the confluent stab wound* **d** *The anastomosed ileal loop is returned to the abdominal cavity*

Simple diverticulectomy as described by Attwood *et al* is inadequate because it is recognized that the bleeding peptic ulceration frequently involves the adjacent ileum, even though the heterotopic gastric tissue lies within the diverticulum Adequate resection can be performed expeditiously with the help of a GIA stapler (US Surgical). With its two forks inserted through two stab wounds on either side of the base of the diverticulum, the instrument enables fashioning of a side-to-side ileal anastomosis. This is then followed by resection of a small segment of the ileum bearing the diverticulum and the now confluent stab wound by a second firing of the GIA placed at right angles to the first one (*Figure 1*). With the aid of an Endo-GIA, much the same procedure can be carried out intra-abdominally, but at the expense of an increased risk of spillage, more wounds for insertion of bowel occlusion clamps and a longer operation time.

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## Quality of life after gastrectomy in patients with carcinoma of the stomach

*Sir*

We read with interest and surprise the article by Korenaga *et al* on quality of life after gastrectomy in patients with gastric cancer (*Br J Surg* 1992, **79** 248–50) First, we would like to congratulate our Japanese colleagues for finally having discovered the issue of quality of life as a relevant endpoint for cancer treatment. The congratulations are even more important since the Japanese have been so refractory to the strategy of randomized clinical trials, despite their huge number of patients with cancer However, their study has several flaws, presents wrong hypotheses and needs extensive comment.

The literature review is incomplete In the introduction, they write that little is known about quality of life in gastric cancer, this is not true There is a randomized clinical trial on reconstruction techniques after radical gastrectomy[1], and our own group in Cologne has conducted two expert conferences on quality of life in surgery[2,3] Furthermore, our group is currently testing a gastrointestinal quality-of-life index, which has already been applied in clinical trials[4,5]

In the *Patients and methods* section, the authors introduce their 16-item survey on food tolerance, body-weight and performance status. Scores were assigned for physical and social well-being by a single interviewer and interpreted as representing the patients' quality of life Our first criticism is that this is a subjective and non-validated way of measuring what the authors think is quality of life. We would go so far as to call it a 'housewife score'. In modern clinical research, there is no room for self-designed non-validated techniques.

Our second criticism regards the concept of quality of life As a result of a consensus conference, methodologists and clinicians look on quality of life as a four-dimensional concept comprising symptomatic, emotional, physical and social components[2,3] The emotional coping with disease is an extremely important aspect of a patient's quality of life As an example, an amputated leg can be either a catastrophe or even a relief for a patient, depending on his or her emotional attitude. The authors do not even mention the domain of emotions

The third criticism concerns the two treatment groups A retrospective separation and historical comparison of partial and total gastrectomy is subject to important bias and needs no further comment

The fourth criticism deals with the fact that the patients have been interviewed by a single – probably subjective – interviewer The problem of observer variation was not addressed

Three statements in the *Discussion* need criticism and comment. In the first sentence, the statement that the influence of operation on quality of life is 'hard to quantify' is incorrect The literature reports the use of validated methods such as the Spitzer index, various visual analogue scales and other tools[6–8] In the second paragraph, the authors write that disturbances in performance status were improved 3 years after operation Since they did not carry out a longitudinal observation study on their patients, this conclusion is inappropriate In the last paragraph, they state that the quality of life is usually better after partial than after total gastrectomy Although this hypothesis is also favoured by our group, evidence is still lacking and is not given by the present study

In future, validated and practical techniques[5] have to be applied in randomized clinical trials to solve such important questions as which resection and reconstruction techniques are best for patients' well-being (provided both techniques offer equal standards of surgical safety).

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## Authors' reply

*Sir*
We thank Dr Eypasch and Professor Troidl for their constructive comments. The purpose of our study was to determine whether a radical $R_2$ gastrectomy prevents the patient's well-being To our knowledge, the present report is the first concerning quality of life in patients undergoing gastrectomy with extensive lymph node dissection (a standard procedure in Japan since the 1960s) Questions and scoring for quality of life were made by several members of the gastric cancer group, and patients were free to select the answers Average scores were calculated for the response to each question and used as the index for the quality of life. Rohrer *et al.*[1] reported the quality of life following repair of abdominal aortic aneurysm using the same analytical method Therefore, this survey seems objective.

Although a retrospective separation of partial and total gastrectomy was present, the effect of historical comparison was thought to be negligible because determination of the type of gastrectomy usually depended on the location of the tumour. Our policy is to undertake total gastrectomy only when a tumour is located in the upper third of the stomach When there is a tumour in the middle and lower third of the stomach, partial gastrectomy is the treatment of choice. This study is a step in the right direction in assessing the patient's well-being Our results suggest that quality of life is usually better after partial than after total gastrectomy. A randomized trial to solve questions such as which resection is best for long-term survival and quality of life in patients with a tumour in the lower two-thirds of the stomach warrants further attention.

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## Easy delivery of the gallbladder in laparoscopic cholecystectomy: a grooved director

*Sir*
We read with interest the Surgical Workshop of Williams *et al.* (*Br J Surg* 1992; 79: 344). At our hospital we have performed over 50 laparoscopic cholecystectomies and use Brodie's grooved director for the easy delivery of the gallbladder through the abdominal incision. It is available in every hospital, and is safe and reusable

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## Proctoscopic polyp delivery after colonoscopic polypectomy

*Sir*
The suggestion of Messrs Chuah and Kelly (*Br J Surg* 1992, **79**: 32) to thread the colonoscope through a proctoscope to remove polyps seems complicated and unnecessary The manoeuvre impedes adequate insufflation and may therefore interfere with visualization of the polyp. We remove the lesion with a grasper or by continuous suction and ask the patient to press at the moment that we retract the tip of the 'scope through the anal canal. In this way the polyp will always follow If a polyp is lost higher up in the descending or sigmoid colon, it can usually be retrieved with an enema.

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## Authors' reply

*Sir*
We were pleased with the interest in our Surgical Workshop shown by Drs Bijnen and de Ruiter, but disagree completely with their conclusions. First, they do not seem fully to have understood our manoeuvre, which is to wait until the severed polyp held in the graspers against the tip of the colonoscope is actually situated in the already inflated lower rectum before railroading in the proctoscope over the endoscope to allow easier removal of the endoscope with polyp in one simple movement.

Second, we just do not seem to be as skilful as our Dutch colleagues in coaxing polyps through the anal sphincters without the help of the proctoscope.

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## Upper thoracic sympathectomy for primary palmar and axillary hyperhidrosis: long-term follow-up

*Sir*
It was with great interest and some concern that we read the recent communication from Hashmonai *et al.* (*Br J Surg* 1992, **79**: 268–71) The authors imply that the supraclavicular approach should remain the method of choice as the long-term results of the newer forms of sympathectomy such as the transthoracic approach are not yet available This advice is both inaccurate and misleading Variations of the thoracoscopic approach have been in routine clinical practice[1] since the 1970s, and indeed endoscopic sympathectomy has been the approach of choice in our own unit for the past 12 years

In a previous paper in this journal[2], we communicated our experience from 1980 to 1987, reviewing 112 cases of palmar and axillary hyperhidrosis treated by endoscopic transthoracic electrocautery of the sympathetic chain. Some differences in outcome deserve comment.

Far from requiring two separate teams of surgeons working simultaneously, in our unit one surgeon operates on each side sequentially, completing both in 30–40 min. The complications of lymphatic duct injury, subclavian artery damage and phrenic nerve injuries were not seen in our series, and to our knowledge have not been reported by others in relation to the endoscopic approach We encountered no case of permanent Horner's syndrome. Indeed, when the endoscopic approach is utilized, the stellate ganglion is protected by a characteristic yellow fat pad This experience has been echoed by others Claes and Gothberg[3] and Banerjee *et al*[4] in their reviews of 100 and 50 patients, respectively, reported no incidence of permanent

Horner's syndrome using the thoracoscopic approach

Hashmonai *et al* make no mention of cosmetic results – surely an important consideration in view of the young age of the treated population and the elective nature of their surgery In our series results were described as 'very good' or 'good' in 95 per cent of patients, with none expressing dissatisfaction with the outcome

Finally, long-term subjective evaluation indicated that, in our series, not only was there good postoperative control of sweating but that this was maintained for the duration of the follow-up (mean 46 (range 3–96) months)

We are convinced that the thoracoscopic approach is the treatment of choice for palmar hyperhidrosis. This view is supported by a considerable body of evidence

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## Authors' reply

*Sir*

We were flattered to learn that Messrs Byrne, Walsh and Hederman found time to read our article and comment We are, of course, well acquainted with their important study In fact early this year, when we started to use the thoracoscopic approach, we were guided by their excellent technique and experience We hope soon to reach the top of the 'learning curve' of the thoracoscopic procedure, it is our intention then prospectively to compare it with our open technique experience Thus in a few years from now we may be able to confirm whether in our hands also the thoracoscopic approach is the treatment of choice for palmar hyperhidrosis

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## Recombinant tissue-type plasminogen activator is superior to streptokinase for local intra-arterial thrombolysis

*Sir*

We were interested to see the report from the Nottingham Group (*Br J Surg* 1992, **79** 272–5) but are concerned that their experience in the use of streptokinase is so different from our own.

Using a strictly controlled protocol[1], administered by the same vascular surgeon and interventional radiologist throughout, our experience of low-dose intra-arterial streptokinase over the past decade has been very satisfactory. In contrast to the experience in Nottingham, we have achieved lysis in 72 per cent of patients, with a lysis time averaging only 25 h, since our early experience[2] Perhaps the late availability of recombinant tissue plasminogen activator (rtPA) means that their streptokinase data refer to their early experience of thrombolytic therapy, since some very long infusion times are reported with this drug in their *Figure 2* We note that the median duration of infusion reported previously by their group when rtPA and streptokinase were compared as part of a contemporaneous study was 22 and 28 h, respectively, which would fit exactly with our own experience[1] and was shorter than the median of 38 h they reported[3] for streptokinase in 1987 We also note that the duration of the history of ischaemia was different in the two treatment groups, with the patients receiving streptokinase having a mean history of 14 (range 1–99) days, the same as in their 1987 publication, while those receiving rtPA had a mean of 10 5 (range 1–49) days

As we have previously described, the risk of major haemorrhagic stroke and serious bleeding is also increased in patients with prolonged infusion In our experience, streptokinase is not only very much cheaper but can be employed with equal effect and safety It is our current policy to reserve rtPA for those patients who are having repeated lysis within 6 months of the administration of streptokinase, or who are known to be sensitive to that agent Using this protocol, streptokinase has provided safe effective lysis in 73 per cent of patients and in 67 per cent given important benefit, as defined by the diagnosis and correction of a significant lesion That benefit has been sustained in 57 per cent of the patients, when followed up for a minimum of 3 years We believe that the advantages of the more modern and highly purified forms of streptokinase now available should not be overlooked

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## Authors' reply

*Sir*

We would like to thank Mr Giddings and Dr Walker for their interest in our report We have two comments on their letter

First, their experience with streptokinase may not be very different from ours Until the two series are reported using the same criteria to define a successful outcome, it is impossible to compare them Similarly, comparisons of the time to lysis between different groups are valid only if the same endpoints for lysis are used. Clearly, for example, if one group has a lower threshold for surgical intervention then such a comparison is invalid.

Second, although they are right to highlight the limited value of non-randomized comparisons between thrombolytic agents, until a sufficiently large double-blind randomized trial is performed these are the only comparisons possible Our study did at least have the virtue of using consistent criteria for defining a successful outcome

There is a clear need for consensus between all vascular centres using thrombolysis on. (1) how the treated patient groups should be described, (2) which endpoints are important and how they should be defined, and (3) which aspects of this treatment have been validated by existing data and which require further trials (For example, almost all centres would probably agree that local thrombolysis is superior to systemic lysis on the basis of existing data )

We hope that the forthcoming meeting of the Thrombolysis Study Group will address these issues

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## Laparoscopic vagotomy: a new tool in the management of duodenal ulcer disease

*Sir*

Medical therapy has dominated the treatment of uncomplicated peptic ulcer disease for the past 15 years. We occasionally encounter patients with intractable ulcer diathesis who prefer to have an operation rather than face life-long medication In this group, the advent of minimally invasive laparoscopic vagotomy may provide an alternative to expensive long-term treatment with $H_2$ antagonists or acid-blockers.

Twelve such patients were offered laparoscopic vagotomy between May 1991 and March 1992. The indication in all cases was intractable disease characterized by multiple relapses despite long-term $H_2$ antagonist therapy (mean 4 (range 2–10) years). The mean age was 39 (range 27–51) years, ten were men and two women. The mean (range) preoperative basal acid output (BAO) and peak acid output (PAO) were 14·6 (4·2–20·5) and 47·4 (36·1–65·1) mmol/h respectively. Six patients underwent posterior truncal vagotomy with anterior highly selective vagotomy, three had bilateral truncal vagotomy with endoscopic dilatation of the pylorus, and two underwent posterior truncal vagotomy with anterior seromyotomy. The last patient had bilateral truncal vagotomy and gastrojejunostomy performed laparoscopically for pyloric stenosis complicating ulcer disease. These techniques have been proven in open surgery to be effective in reducing acid output[1–3]. The choice of the type of vagotomy depended on the configuration of the anterior vagal trunk and its branches. The mean duration of the operation was 150 (range 120–210) min After operation, feeding was resumed on the third day and patients discharged on the fourth. There were no major complications. One patient who underwent posterior truncal vagotomy and anterior highly selective vagotomy had poor gastric emptying requiring endoscopic pyloric dilatation. The mean (range) postoperative BAO and PAO were 4·1 (3·1–7·3) and 16·5 (2·6–25·7) mmol/h, respectively.

This minimally invasive procedure is safe and associated with little postoperative discomfort, a shorter convalescence and good cosmesis. Larger series with long-term follow-up are required to test the efficacy of this approach, but early experience suggests that laparoscopic vagotomy may provide the solution for the group of patients with chronic intractable ulcer diathesis[4].

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1. Taylor TV, Macleod DAD, Gunn AA *et al* Anterior lesser curve seromyotomy and posterior truncal vagotomy in the treatment of chronic ulcer disease. *Lancet* 1982, **ii** 846–9.
2. Hill CL, Barker MCJ. Anterior highly selective vagotomy with posterior truncal vagotomy: a simple technique for denervating the parietal cell mass. *Br J Surg* 1978; **65**: 602–5.
3. Taylor TV, Holt S, Heading RC. Gastric emptying after anterior lesser curve seromyotomy and posterior truncal vagotomy. *Br J Surg* 1985; **72**: 620–2
4. Mouiel J, Katkhouda N. Laparoscopic truncal and selective vagotomy. In: Zucker KA, Bailey RW, Reddick EJ, eds. *Surgical Laparoscopy*. St Louis: Quality Medical Publishing, 1991 263–79.

## Predeposit autologous blood transfusion in patients with colorectal cancer: a feasibility study

*Sir*

In their recent article (*Br J Surg* 1992, **79**. 355–7) Harrison and colleagues have utilized autologous donation as an ingenious device to circumvent the ethical difficulties of studying the effects of transfusion on patients with colorectal cancer. Unfortunately, in their prospective study they have come to the same conclusion as we arrived at in a recent retrospective analysis of blood use in a general surgical context[1], namely that the operations they were performing did not use blood on a sufficient scale to justify the effort of autologous donation

We analysed all general surgical operations and found that very few would be suitable for the offer of autologous donation, on the basis of the average quantity of blood transfused However, within general surgery the operations of abdominoperineal resection of the rectum and gastrectomy would be suitable, because of broadly predictable transfusion requirements. While most units will not perform sufficient numbers of these procedures to justify the setting up of an autologous donor service, other surgical specialties carry out operations where blood loss is predictably high, such as transurethral surgery or hip replacement. If autologous donation is to become feasible in general surgery, we must cooperate with other surgical specialties to achieve cost effectiveness. Perhaps this would also allow the elucidation of the nature of the effect of transfusion on survival.

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1 Jaffray B, King PK, Basheer AMM, Gillon J. Efficiency of blood use in general surgery and prospects for autologous donor schemes. *Ann R Coll Surg Engl* 1991, **73**: 235–7.

# Book reviews

## An Atlas of Rectal Endosonography

*J. Beynon, G Feifel, U. Hildebrandt and N. J McC Mortensen. 248 × 170 mm Pp 111 Illustrated 1991 Berlin Springer-Verlag DM 175.*

Rectal endosonography is a precise way of measuring rectal cancer invasion and is much more accurate than clinical examination. Enlarged lymph nodes can be seen but they do not necessarily contain cancer, smaller lymph nodes cannot be seen. It can be argued that exact knowledge of the depth of primary tumour penetration will allow better decision making when contemplating a local excision The counter-argument is that local excision is rarely performed (five were carried out at St Mark's Hospital in the 2 years 1989 and 1990) and the excised specimen can be assessed for depth of primary tumour penetration as accurately by the pathologist, who can advise on whether anything further needs to be done (which rarely, if ever, has been the case)

Ultrasonography can also detect local recurrence, but whether this facility is clinically useful is open to conjecture (cf the issue of regular carcinoembryonic antigen testing) because local recurrence is often coupled with distant metastases Endoscopically mounted ultrasonographic equipment is becoming available which would extend this potential follow-up application

Ultrasonography can also be used in the anus, where it is accurate in assessing sphincter injuries (but then, so is digital assessment). It can be helpful in some cases of anal fistula, although here it has limitations as supralevator and ischiorectal collections are difficult to see with the anal probes.

This atlas contains 78 pages of good-quality figures, which are mainly sonograms, and 26 pages of text It has been compiled by world experts, in the manner of experts they are able to share the practical difficulties and give useful tips It is essential reading for anyone in this field embarking on research or offering a clinical service

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## Surgical Treatment of Anal Incontinence

*C V Mann and R E Glass 276 × 197 mm. Pp. 160. Illustrated. 1991 Berlin Springer-Verlag DM 290.*

This book has been devoted to the surgical management of anal incontinence and comprehensively covers the whole field There are chapters on the essential anatomy and physiology of anal continence The section on abdominal techniques covers the various operations for rectal prolapse. This is followed by anterior and posterior perineal repairs, circumanal techniques, peranal procedures, overlapping repairs, the management of congenital anal deformity, repair of the traumatically injured sphincters and, finally, repair of rectovaginal fistulae The illustrations are superb and in themselves comprehensive Each one sequentially takes the reader through the stages of the operative management of the individual condition The chapter on the management of anal deformities is of very high quality. It critically evaluates the various techniques and gives good guidance as to what should or should not be attempted In all the sections, case selection has been carefully discussed, as has postoperative care

I had few criticisms of this text It was a little surprising to see the Thiersch wire procedure for incontinence and prolapse being covered in such detail as I believe this is an outmoded technique that has little place in the current management of continence disorders The Ripstein technique for rectal prolapse was described using anterior encirclement of the rectum, which has largely been abandoned because of the problems of obstruction, this has been clearly pointed out in the text.

In the section on abdominal rectopexy with left-sided colonic resection as described by Goldberg, the authors stress that this operation should not be carried out in patients with weakened sphincters and advise against resection as part of the prolapse repair This is somewhat contrary to published experience, where continence rates following the resection rectopexy as described by Goldberg are remarkably good

I especially enjoyed the chapter on management of congenital anal deformity, which guides the reader through the possible and the inadvisable Once again, the illustrations are superb and those unfamiliar with these areas should obtain excellent guidance from the text and illustrations Overall, this is a superb text with much to offer the experienced colorectal surgeon It is a superb reference text for those embarking on a practice in specialist colorectal surgery and is to be highly recommended

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## Clinical Gastroenterology

*R. C N Williamson and J N Thompson 233 × 154 mm. Pp 935 Illustrated 1991 London Baillière Tindall £27 50.*

Between the covers of this slim volume are a number of well chosen, highly selected topics that are of relevance to all doctors working in the specialty of clinical gastroenterology, i e surgeons, physicians and radiologists. Surgeons will discover a rich seam of knowledge usually not well covered in the surgical literature.

The first two chapters are complementary: a clear, detailed description of hepatobiliary emergencies from the physician's standpoint, followed by surgical emergencies in liver disease I was particularly impressed with the clear line drawings depicting the different forms of portacaval shunt Both chapters are well referenced, covering the most up-to-date literature. Pancreatitis is analysed from the therapeutic endoscopist's viewpoint with a well balanced literature review and sound practical advice The role of surgery in pancreatitis is covered in a more anecdotal fashion by authors from a unit with a large experience and excellent results Their recommendations are, therefore, of great practical value, although clearer guidelines on the indications for surgery would have been helpful For acute cholecystitis, radiological aspects were explained very clearly and their limitations fairly pointed out, and the surgical management has as good a coverage as can be read in any major textbook. The chapter on nutritional support was a little disappointing· few of the references were of recent origin and one was left with the impression that nutritional support had not moved on in the past 5 years, whereas in fact there has been increasing interest in the use of peripheral nutrition The chapters on gastrointestinal emergencies in the tropics and on human immunodeficiency virus infection fascinated and illuminated this reviewer and I am sure that other readers will find them just as stimulating For completeness the book was rounded off by a small contribution on paediatric emergencies, which I am sure is adequate for the general surgeon, although ambitiously compressed into 13 pages

At the giveaway price of £27 50 this volume can be highly recommended to trainees at all levels and specialists wishing to have an overview of the topics outlined.

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## Angiography and Interventional Radiology

*R J. Rosen and J Noshei 259 × 196 mm. Illustrated. 1991 Philadelphia J B. Lippincott £45*

This compact 100-page introduction to angiography and interventional radiology from the USA is economically priced at £45 There are 263 radiographs with almost 50 colour plates The illustration quality is generally very high, the colour plates being particularly outstanding Because of the large number of illustrations, the text is necessarily short. Since there is no preface, I am not sure at which professional group this book is aimed The text is too basic and with insufficient detail for radiologists, although the wealth of illustrations would be of some value to the angiographer/interventionalist in training House officers, radiographers and nurses handling patients undergoing interventional procedures should find it easy to read and useful

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Although ultrasonography and computed tomography are mentioned, the reader might get a false impression of the diagnostic value of angiography compared with these modalities. The recommended roles of angiography in planning treatment of abdominal aortic aneurysm and in the diagnosis of pulmonary embolism are not in accordance with current UK practice. Thrombolytic therapy is dealt with in only half a page of text In the biliary tract section, there is no acknowledgement of the very major role of endoscopic retrograde cholangiopancreatography in diagnosis and management, the short section on lymphography is largely obsolete, and the section on biopsy technique not up to date The bibliography is very short with only one reference more recent than 1987 Despite these shortcomings, this book may be worth a place in the radiology or surgical library.

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## The Management of Major Trauma

*C. Robertson and A D Redmond. 240 × 155 mm. Pp. 190 Illustrated. 1991. Oxford. University Press. £12·95.*

This is the first of a series of handbooks in emergency medicine to be published by Oxford University Press for junior staff working in accident and emergency departments. The book is divided into four parts. The first, on the epidemiology of trauma and primary management, is followed by chapters on 'System assessment'. The third section covers the pathophysiology of trauma and patient transport and the fourth is devoted to practical procedures and bereavement counselling.

The assumption that behind this rather unconventional layout is a new approach to the integration of trauma care is not borne out by closer inspection. Some chapters are indeed of a high standard – for example the section on chest trauma is crisp, logical and clearly pitched at the accident and emergency trainee. However, many are poorly constructed, vary in depth of detail, and do not follow the didactic approach promised in the introduction.

Of more importance is the general lack of cohesion and consistency For example, on page 36 the trainee reads that central venous catheters 'have no place in the initial stages of resuscitation.' Yet on page 123 a 'key point in volume replacement' is the frequent measurement of *inter alia* central venous pressure The indications for chest drain insertion in the collapsed, injured patient follow conventional teaching in the chapter on chest injuries, but the advice in an earlier chapter on initial resuscitation is positively commended as being far more 'aggressive' When looking for guidance on the use of radiographs in major trauma, the reader will find a crisp list on page 41, but conflicting advice on page 84

It may be possible to resolve some of these issues in a second edition, but my main anxiety about the text is a complete absence of reference to advanced trauma life support courses. Some of the recommendations in the book conflict with advanced trauma life support guidelines This can lead only to confusion and it is to be hoped that in any future editions the authors will strive to achieve in print what they already practice clinically – a coordinated system of care based on sound physiological principles and priorities

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## Colonic Diverticular Disease

*M. C. Veidenheimer and P. L. Roberts. 241 × 161 mm Pp. 174 Illustrated. 1991 Oxford· Blackwell Scientific £49 50.*

Useful prefaces begin with provenance and aim, and finish with thanks. This book ends in good form but opens with disturbing vagueness. Apparently pregnant with meaning, on closer scrutiny the opening sentences reveal a verbal pseudocyesis, a Sellarsesque rigmarole of grammatical non sequiturs

That they should start on such an uncertain note may reflect the authors' ambiguity of purpose, for can they really think a separate whole book an appropriate vehicle for informing medical students and house officers (part of their stated target) about colonic diverticular disease? Even registrars and consultants might consider a chapter in a general work sufficient. They hope to 'present a ready reference'. If readiness here means low costs their objective has surely been achieved. Both text and illustrations are inexpensively produced – and to the detriment of both. Even good writing is enervated by dull type and the radiographs are of poor quality, losing the illustrative features altogether in one or two cases.

This said, and other valid unmentioned criticisms apart, the book is short and amply illustrated and one author is a recognized authority. Practising surgeons – the only sensible readership – will find it quick and easy to bring themselves reliably, if not particularly inspiredly, up to date.

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## Operative Surgery

*R Calne and S. G. Pollard 444 × 257 mm. Illustrated. 1992. London· Gower Medical.*

This book is written essentially by trainee surgeons for trainee surgeons It describes the commonest operations likely to be performed or learned by surgeons in training and covers general surgery, trauma and urology but excludes orthopaedics, plastic surgery and neonatal surgery. For each section there is a description of relevant anatomy, preoperative assessment, and key points of operative technique. Where there are special risks these are highlighted. To illustrate the operative procedures there are very clear coloured line drawings, which have been taken from photographs Descriptions are personal, which is nice, but I feel variations or opposing views could have been covered, for example, the Shouldice repair of inguinal hernia is not mentioned at all. Recent developments are included but the more established procedures lack sufficient detail For example, in the section on femoropopliteal bypass minimal mention is given to prosthetics and none to vein cuffs, which are certainly as well established as laparoscopic cholecystecomy (which has a whole chapter).

This book will appeal principally to surgical trainees studying for part II FRCS and is likely to find its way into operating theatre libraries. There are a number of similar works on operative surgery but for me the strength of this one lies in the illustrations. I am sure it will be popular.

**S. Parvin**

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# Publisher's note

Incorrect information supplied to the Journal unfortunately meant that one of the books reviewed in the May issue (*Br J Surg* 1992; 79: 473) was attributed to the wrong originating publisher. The correct originating publisher and UK price are given below.

**A Colour Atlas of Endovascular Surgery**

*R. A. White and G H. White. 216 × 279 mm. Pp 200 Illustrated 1991.*
*London· Chapman and Hall. £70.*

The Journal apologizes for any confusion caused.

# Notices and announcements

8–9 October 1992
**Second GI Tract Laparoscopic Surgery International Meeting**
*Liège, Belgium*
*Information* Catherine Marissiaux, Clinique St-Joseph, Chirurgie de l'Appareil Digestif, Rue de Hesbaye 75, B-4000 Liège, Belgium

11–16 October 1992
**American College of Surgeons Annual Clinical Congress**
*New Orleans, Louisiana, USA*
*Information* American College of Surgeons, 55 East Erie Street, Chicago, Illinois 60611-2797, USA

15–16 October 1992
**European School of Oncology 10th Anniversary Events**
*Milan, Italy*
*Information* European School of Oncology, Via Venezian 18, 20133 Milan, Italy

23 October 1992
**Symposium – Extracranial Carotid Artery Surgery: Including Prevention of Stroke**
*London, UK*
*Information* Mrs Louise Brooks, Meadox UK Ltd, Matthew House, Matthew Street, Dunstable LU6 1SD, UK

27 October–4 November 1992
**Anaesthesia and Surgical Intensive Care: Controversies and Conflicts**
*Bristol, UK*
*Information* Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

4–6 November 1992
**Vascular Surgical Society of Great Britain and Ireland Annual Meeting**
*London, UK*
*Information* Mr P L Harris, VSS Secretary, Vascular Unit, Broadgreen Hospital, Thomas Drive, Liverpool L14 3LB, UK

4–8 November 1992
**American Association for Cancer Research – Genetics of Cancer**
*Hilton Head Island, South Carolina, USA*
*Information* American Association for Cancer Research, Public Ledger Building, 620 Chestnut Street, Suite 816, Philadelphia, PA 19106-3483, USA

5–6 November 1992
**European Workshop on Digestive Surgery**
*Brussels, Belgium*
*Information* Conference Services, 3/17 Avenue de l'Observatoire, B-1180 Brussels, Belgium

6–7 November 1992
**International College of Surgeons 38th Annual Meeting of the Japan Section – 'Controversies in Surgery'**
*Tokyo, Japan*
*Information* Professor K. Kimura, Department of Surgery, Tokyo Medical College, 6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo, Japan

7–10 November 1992
**17th International Congress of the European Society for Medical Oncology**
*Lyon, France*
*Information* Secretariat, ESMO-92, Centre Léon Bérard, 28 Rue Laennec, 69373 Lyon, France

8–10 November 1992
**Society for Minimally Invasive Therapy Fourth Annual World Conference**
*Dublin, Ireland*
*Information* Mr N N Williams, Department of Surgery, Mater Hospital, 47 Eccles Street, Dublin 7, Ireland

9–13 November 1992
**Annual Course in Hepatobiliary and Pancreatic (HPB) Surgery**
*London, UK*
*Information* Jacqui Searle, Wolfson Conference Centre, Royal Postgraduate Medical School, Hammersmith Hospital, London W12 0NN, UK

13 November 1992
**Symposium on Liver Transplantation**
*London, UK*
*Information* Mr N. A. Habib, Wolfson Conference Centre, Royal Postgraduate Medical School, Hammersmith Hospital, London W12 0NN, UK

15–18 November 1992
**Update and Future Trends in Fibrin Sealing in Surgical and Non-surgical Fields**
*Vienna, Austria*
*Information* Univ Prof G Schlag, Ludwig Boltzmann Institute for Experimental and Clinical Traumatology, Donaueschingenstraße 13, A-1200 Vienna, Austria

15–21 November 1992
**Advances in Cancer Treatment**
*London, UK*
*Information* Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

16–20 November 1992
**Research Methods in Surgery**
*London, UK*
*Information* Jacqui Searle, Wolfson Conference Centre, Royal Postgraduate Medical School, Hammersmith Hospital, London W12 0NN, UK

16–21 November 1992
**XXVIII World Congress of the International College of Surgeons**
*Cairo, Egypt*
*Information* EMECO Travel, 2 Talaat Harb Street, PO Box 1294, Cairo, Egypt

25–28 November 1992
**Recent Advances in Anaesthesia, Pain, Intensive Care and Emergency**
*Trieste, Italy*
*Information* Trieste Traduzioni Congressi, Via C Battisti 1, 34125 Trieste, Italy

3–5 December 1992
**Special International Columbus Meeting on Surgical Oncology**
*Genoa, Italy*
*Information* Italiana Congressi, Via P E. Bensa 2/6A, 16124 Genoa, Italy

4–5 December 1992
**8th International Steglitz Paediatric Surgical Congress: Endoscopic Surgery in Children**
*Berlin, Germany*
*Information* Dr F Schier, Kinderchirurgie, Universitatsklinikum Steglitz, Hindenburgdamm 30, 1000 Berlin 45, Germany

8–10 December 1992
**Seventh International Workshop on Therapeutic Endoscopy**
*Hong Kong*
*Information* Dr S. Chung, Combined Endoscopy Unit, Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong

10–11 December 1992
**Reconstruction in Surgical Oncology**
*Genoa, Italy*
*Information* Anna Guida, Istituto Nazionale per la Ricerca sul Cancro, Viale Benedetto XV, 10-16132 Genoa, Italy

3–6 January 1993
**Postgraduate Course in Gastroenterology**
*Oxford, UK*
*Information* Dr D P Jewell, Radcliffe Infirmary, Oxford OX2 6HE, UK

7–8 January 1993
**Surgical Research Society Meeting**
*London, UK*
*Information* Professor J. R. Farndon, Department of Surgery, Bristol Royal Infirmary, Bristol BS2 8HW, UK

5 February 1993
**Transjugular Intrahepatic Portocaval Shunts**
*Toulouse, France*
*Information* Service d'Hépato-Gastro-Entérologie, CHU Purpan, 31059 Toulouse, France

8–10 February 1993
**Child Safety in Southern Africa**
*Cape Town, South Africa*
*Information* Deborah McTeer, Postgraduate Medical Centre, UCT Medical School, Observatory 7925, Cape, South Africa

18–20 February 1993
**Colorectal Disease in 1993: an International Exchange of Medical and Surgical Concepts**
*Fort Lauderdale, Florida, USA*
*Information* The Cleveland Clinic Educational Foundation, Department of Continuing Education, 9500 Euclid Avenue, Room TT-31, Cleveland, Ohio 44195-5241, USA

21 February 1993
**Phlebology Review**
*Lake Buena Vista, Florida, USA*
*Information* North American Society of Phlebology, 511 Encinitas Boulevard, Suite 111, Encinitas, California 92024, USA

# SURGERY

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# Instructions to authors

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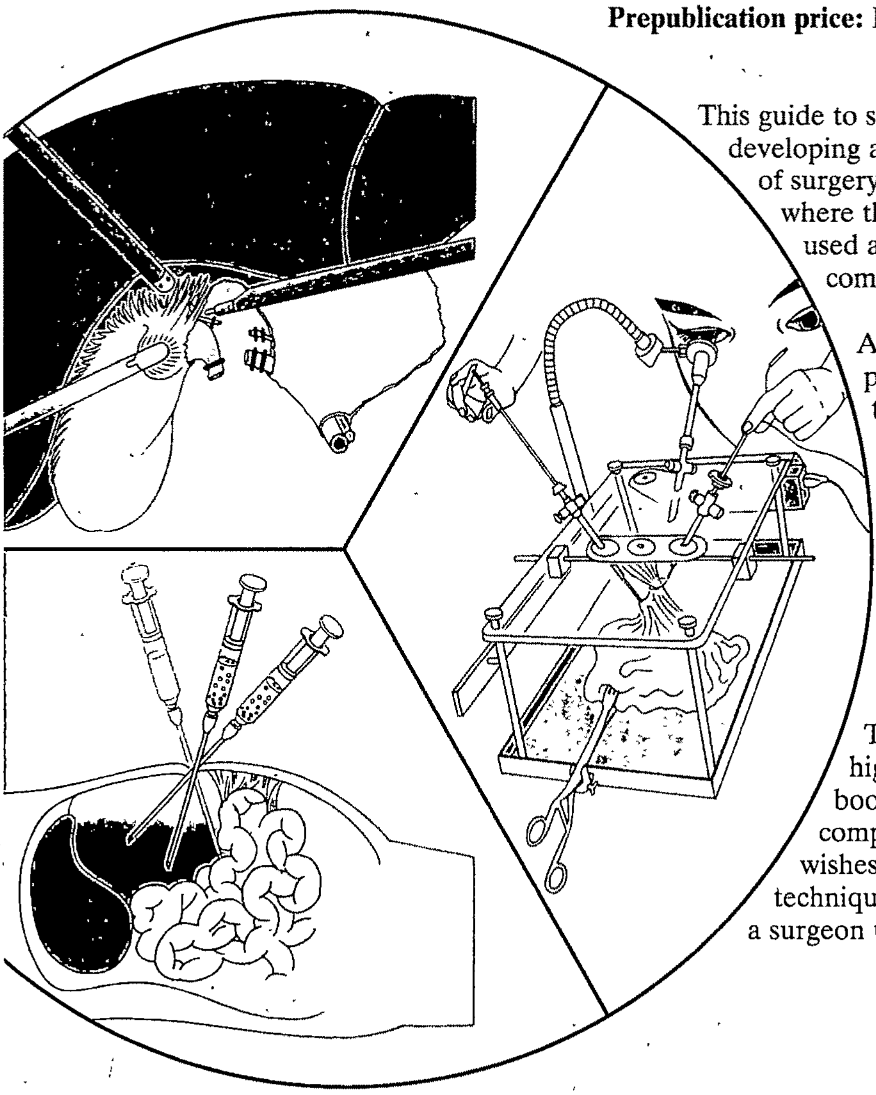

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